"A COMPARATIVE STUDY ON THE EFFICACY OF METHOTREXATE VS DAPSONE VS ASST (AUTOLOGOUS SERUM SKIN THERAPY) FOR TREATMENT OF CHRONIC URTICARIA"

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(BRANCH XX)

MADRAS MEDICAL COLLEGE

THE TAMILNADU DR. M.G.R. MEDICALUNIVERSITY

CHENNAI, INDIA.

APRIL 2016

CERTIFICATE

Certified that this dissertation titled **"A COMPARATIVE STUDY ON THE EFFICACY OF METHOTREXATE VS DAPSONE VS ASST (AUTOLOGOUS SERUM SKIN THERAPY) FOR TREATMENT OF CHRONIC URTICARIA "**

is a bonafide work done by **Dr.M. MEENAKSHI ,** Post graduate student of the Department of Dermatology, Venereology and Leprosy, Madras Medical College, Chennai – 3, during the academic year 2013 – 2016. This work has not previously formed the basis for the award of any degree.

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The dissertation entitled **"A COMPARATIVE STUDY ON THE EFFICACY OF METHOTREXATE VS DAPSONE VS ASST (AUTOLOGOUS SERUM SKIN THERAPY) FOR TREATMENT OF CHRONIC URTICARIA "** is a bonafide work done by **Dr. M. MEENAKSHI** at Department of Dermatology, Venereology and Leprosy, Madras Medical College, Chennai – 3, during the academic year 2013 – 2016 under the guidance of **Professor Dr. V. SAMPATH, M.D.,** Professor, Department of Dermatology, Madras Medical College, Chennai -3. This dissertation is submitted to The Tamil Nadu Dr. M.G.R. Medical University, Chennai towards partial fulfillment of the rules and regulations for the award of M.D Degree in Dermatology, Venereology and Leprosy (BRANCH – XX)

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DECLARATION

I, **Dr. M.MEENAKSHI** solemnly declare that this dissertation titled **"A COMPARATIVE STUDY ON THE EFFICACY OF METHOTREXATE VS DAPSONE VS ASST (AUTOLOGOUS SERUM SKIN THERAPY) FOR TREATMENT OF CHRONIC URTICARIA "** is a bonafide work done by me at Madras Medical College during 2013-2016 under the guidance and supervision of **Prof. K.MANOHARAN, M.D., D.D.,** Professor and Head, Department of Dermatology, Madras Medical College,Chennai-600003.

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LIST OF ABBREVIATIONS

CU	- -	Chronic Urticaria
HLA	- -	Human Leucocyte Antigen
IgE	- -	Immunoglobluin E
TNF	- -	Tumor Necrosis Factor
LT	- -	Leukotrienes
PGD	- -	Prostaglandins
NSAID	- -	Non Specific Anti Inflammatory Drugs
DG	- -	Dermographism
An	- -	Anemia
Es	- -	Esonophilia
ASST	- -	Autologous serum skin test/therapy
UAS	- -	Urticarial Activity Score
DLQI	- -	Dermatological Life Quality Index

ABSTRACT

A COMPARATIVE STUDY ON THE EFFICACY OF METHOTREXATE VS DAPSONE VS ASST (AUTOLOGOUS SERUM SKIN THERAPY) FOR TREATMENT OF CHRONIC URTICARIA

INTRODUCTION

Chronic urticaria (CU) is a common skin disorder affecting 15–20% people in the general population.Pathogenesis of CU is unclear and possible causes may include chronic infections, allergy to certain food or food additives, anxiety, and autoantibody production against IgE receptor. It remains a major problem in terms of etiology, investigation, and management and causes comorbidity and high cost to the health care system.

AIMS & OBJECTIVES

1. To compare the efficacy of treatment of dapsone, methotrexate and ASST (Autologous Serum Skin Therapy) for chronic urticaria.

2. To determine the prevalence of auto immune urticaria in patients with chronic urticaria.

3. To determine the remission rates for each treatment

4. To assess the improvement in UAS (Urticaria Activity Score) & DLQI (Dermatology Life Quality Index) with treatment.

MATERIALS & METHODS

It is prospective and comparative study. Around 120 patients with chronic urticaria were selected from the patients attending psoriasis out-patient clinic in Department of Dermatology, Madras Medical College. All patients will be explained about the disease, benefits & possible side effects of treatment. Informed written consent will be obtained from all patients before initiation of treatment. The patients will be randomly allotted to any one of the following four treatment groups after calculating their Urticarial Activity Score (UAS) & Dermatology Life Quality Index (DLQI).Group A will comprise patients who will be given oral Dapsone 50 mg for a period of 12 weeks.Group B will comprise patients who will be given oral Methotrexate 10 mg per week for a period of 12 weeks. Group C will comprise patients who will be given Treated with ASST (Autologous Serum Skin Therapy) – 2ml of autologous serum deep intramuscular injection once a week for 9 weeks.In addition to these, patients in all the groups will be prescribed Antihistamines. Group D will be the control group who will receive only Antihistamines. Patients were then divided into three categories based on their DLQI and UAS scores intoGood Responders, Average Responders & Poor Responders.

RESULTS & DISCUSSION

The ASST group patients showed the maximal reduction in DLQI score between baseline and the follow up value at six months with a drop of more than ten points seen even in patients with poor response. ASST group patients also had a high reduction inDLQI score soon after initiating treatment, with near complete recovery seen as soon as completing treatment. In the dapsone group, the initial response is lower than that of ASST and the net reduction is also lower than that of ASST. The end points are comparable in each response group separately but is not reliable as fewer patients showed good response. In methotrexate group, the initial response was lower than both dapsone and ASST, with symptomatic improvement becoming evident only towards the end of treatment or even after treatment. The net reduction in DLQI score at the end of six months was similar to dapsone group. There is a statistically significant difference in response to treatment to all three groups when compared to control, with it being highly significant in the ASST group. On comparing ASST with dapsone or methotrexate, there is again a statistically significant difference in response while there was no statistically significant difference when comparing dapsone and methotrexate.

CONCLUSION

1. Proper evaluation is mandatory to find out the presence of precipitating factor and if present, management of the same

2. ASST can be considered as a first line of treatment, in patients with chronic urticaria, especially in those who are positive for Autologous Serum Skin Test. The preferred regimen being 2ml of autologous serum given as deep intramuscular injections once a week for nine weeks

3. Dapsone can be considered for patients refractory to treatment. The regimen being 50mg daily for a period of 12 weeks.

4. Methotrexate is recommended as last resort, in patients who are refractory to other modalities of treatment. Side effects profile and its contraindication in patients with haematological problems, restrict its more common usage

5. A randomized, controlled study with prolonged follow up and involving much more modalities of treatment is necessary to devise an accepted management protocol for patients with chronic urticaria.

INTRODUCTION

Chronic urticaria (CU) is a common skin disorder affecting 15–20% people in the general population. Based on its duration, frequency and causes, CU can be classified into three clinical subgroups, spontaneous (80%), physical (10%) and special forms (10%). Chronic spontaneous urticaria (CSU), also known as chronic idiopathic urticaria, is characterized by spontaneous occurrence of wheals without an obvious stimulus lasting for more than 6 weeks. Pathogenesis of CSU is unclear and possible causes may include chronic infections, allergy to certain food or food additives, anxiety, and autoantibody production against IgE receptor.

Ordinary chronic urticaria is appropriately termed as a “Cinderella” disease with a capricious course and a demoralizing response to treatments. There are no guaranteed means of controlling attacks. It can be difficult to determine the appropriate medication, as the condition is intermittent and outbreaks also typically clear up without any treatment.

Chronic Urticaria remains a major problem in terms of etiology, investigation, and management and causes comorbidity and high cost to the health care system. In our study, we are comparing the use of ASST, Dapsone and Methotrexate for the treatment of resistant chronic urticaria. In addition, the clinio-etiological patterns of the disease were ascertained. So, these study findings will play an important role to determine treatment protocols for patients with chronic urticaria

Review of Literature

REVIEW OF LITERATURE

2.1 Definitions [1,2]

Urticaria is defined as a skin lesion consisting of a wheal-and-flare reaction where the localized intracutaneous edema (wheal) is surrounded by an area of redness (erythema) that is typically pruritic. Individual lesions last as briefly as 30 minutes to as long as 36 hours. They can be as small as a millimeter or 6–8 inches in diameter (giant urticaria). They blanch with pressure as the dilated blood vessels are compressed, which accounts for the central pallor of the wheal.

Weals , also known as 'nettle rash' or hives is a transient, well-demarcated, superficial erythematous or pale swellings of the dermis, very itchy and are associated with a surrounding red flare.

Angio-oedema also called as angioneurotic oedema is a swelling of the deeper dermis subcutaneous and submucosal tissues. They are painful rather than itchy, poorly defined, and pale or normal in colour.

Anaphylaxis, is an acute, severe, life-threatening, generalized or systemic hypersensitivity reaction. It consists of a combination of symptoms and signs, including diffuse erythema, pruritus, urticaria and angio-oedema, hypotension and difficulty in breathing.

2.2 Historical Background [3-5]

Urticaria, has a long and rich history. Many cultures have described urticaria and the disorder has had many names. The earliest description of the disease is found in "The Yellow Emperor's Inner Classic",by Huang Di Nei Jing, written between 1000 BC and 200 BC . In 10th century B.C. it was called 'Feng Yin Zheng' in China. In 4th century B.C., Hippocrates noted similarities between urticaria, stinging nettles, and insect bites and called the condition as 'knidosis' (nettle rash). 'Uredo,' 'essera' (Arabic for elevation), 'urticatio' (derived from the Latin urere; to burn), and 'scarlatina urticaria' have all been used.

In 18th century, urticaria was compared with the stinging and burning of a nettle (Urtica dioica). William Cullen was the first to use the term urticaria in 1769. Many theories about the pathogenesis of urticaria have been described - a humoral theory , a metereologic theory in, and a menstrual theory in 1864.

Different types of urticaria were described by willan and bateman:

- Urticaria febrilis - patient has fever and abdominal pain for some days before the skin lesions appear.
- Urticaria evanida - new lesions can continue to appear for many months or years and mainly itching at night
- Urticaria perstans - single central weal remains for some days and feels hard. The initial reddening around the weal disappears early.

✓Cold urticaria - described by Frank in 1792.

✓Solar urticaria - described by Borsch in 1799

✓Factitial urticaria -described by Heberden in 1767 and Gull coined the name factitious urticaria in 1859

✓Angio-oedema -described 1586 by Marcello Donati

✓Hereditary angio-oedema - Osler in 1885.

✓Urticaria caused by heat and mental or physical exertion was published in 1924 in by Duke.

✓Pressure urticaria - described by Urbach and Fasal in 1929.

✓Aquagenic urticaria - Shelley and Rawnsley in 1964

✓Adrenergic urticaria - Shelley & Shelley in 1985.

✓Urticaria pigmentosa - Edward Nettleship.

✓Sangster named urticaria pigmentosa and Unna discovered the mast cells in the lesions.

2.3 Epidemiology [6-8]

Urticaria affects 15%–20% of the population. Urticaria is a common problem, with a point prevalence of 0.1%. Lifetime prevalence of chronic urticaria varies from 0.05% to 23.6% in the general population, but a range of 1–5% seems more realistic. There is no racial variation in the incidence. Overall, urticaria is more common in women, with a female : male ratio of approximately 2:1 for chronic urticaria. Urticaria affects people of all age groups, but usually those in the second and third decade of life. Hereditary angioedema has an autosomal dominant inheritance pattern and occurs in approximately 1:150 000.

An Indian study of 100 patients with urticaria found that 10% had urticaria due to bacterial infection; 69%, due to worm infestation; 6%, drug induced; 3%, insect bites; 2%, cold urticaria; 4%, cholinergic urticaria; and 3%, dermographism. Inhalants and food were responsible in 35% and 25% cases respectively. Among inhalants, 26% of cases were due to pollen; 9%, fungi; and 10% due to house dust and buffalo dander. In 6% of the cases, no cause could be detected. Among 500 cases of urticaria in another Indian study, 37% of the patients were suffering from physical urticaria, including 16.4% due to symptomatic dermographism; 10.8%, cholinergic urticaria; 8.4%, cold urticaria; 0.7%, solar urticaria; and 0.5%, both pressure and delayed cold urticaria. Hereditary angio-oedema, the autoinflammatory syndromes (cryopyrin-associated autoinflammatory syndrome) and a other rare physical urticarias are inherited as autosomal dominant traits. There is a highly significant linkage of human leukocyte antigen (HLA) DRB1*04 (DR4) and its associated allele DQB1*0302 (DR8) with histamine-releasing autoantibody-positive chronic ordinary urticaria. Polymorphisms of the FcRI promoter and leukotriene C4 synthetase genes have been associated with aspirin-sensitive urticaria.

2.4 Histopathology [9-13]

Edema is usually present in the superficial portion of the dermis in urticaria whereas it appears in the deeper dermis and subcutaneous tissue in angioedema. Dilated venules with endothelial swelling with minimal inflammatory cells are seen in acute urticaria, while a perivascular and interstitial infiltration of

lymphocytes, eosinophils and neutrophils is seen in chronic urticaria. In hereditary angioedema, only subcutaneous and submucosal edema is seen, but there are no inflammatory cells.

Immunoglobulin and complement proteins are not detected by direct immunofluorescence (DIF) tests. Major basic protein, a cytotoxic molecule from eosinophilic granules, is found in the dermis of skin lesions of chronic urticaria, delayed pressure urticaria, and solar urticaria.

An early leukocytoclastic vasculitic picture characterized by neutrophilic infiltration in and around dermal blood vessels, leukocytoclasis, minimal fibrin deposits and extravasation of erythrocytes is seen in urticarial vasculitis. DIF test showsprominent granular deposits of immune complexes along with dermoepidermal junction and perivascular areas. Positive immunofluorescence is seen more commonly in cases of urticarial vasculitis having a low complement level. Necrotizing vasculitis of venules has been found in dermographism, cold urticaria, pressure urticaria and solar urticria

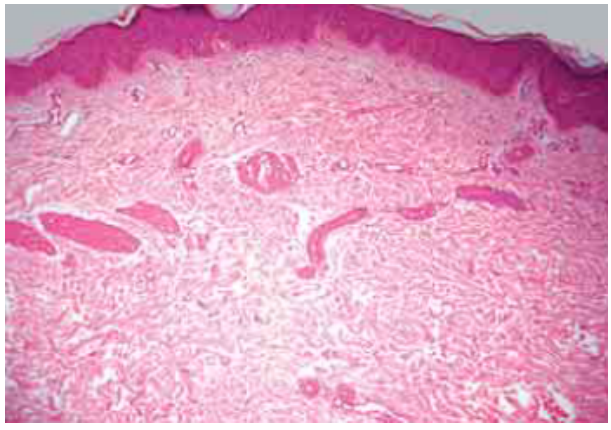


FIG 1. Histopathological picture of urticarial lesion

2.5 Pathogenesis [14-20]

Pathomechanisms of different urticarias

1. Mast cell-dependent urticarias:

➢ Immunologic:

- Autoimmune urticaria (autoantibodies against FcRI or IgE)
- IgE-dependent (allergic, mostly acute urticaria)
- Contact urticaria (allergic, IgE-dependent)
- Children with atopic dermatitis sensitized to environmental allergens like grass, animals and food
- Glove-wearers having allergy to latex

➢ Non-immunologic:

- Direct mast cell-releasing agents (e.g. opiates, vancomycin, polymyxin, some radiocontrast media, C5a, substance P, stem cell factor and some foods like strawberries)
- Contact urticaria (nonallergic, certain histamine liberating chemicals that degranulate mast cells, e.g. dimethylsulfoxide and cobalt chloride)
- Aspirin and other NSAIDs, dietary pseudoallergens

2. Mast cell-independent urticarias:

➢ Immunologic:

- Complement and kinin dependent (C1 esterase inhibitor deficiency urticarias)

➢ Non-immunologic:

- ACE-inhibitors induced urticaria (believed to be from inhibition of endogenous kinase)
- Contact urticaria (nonallergic, due to direct effect of urticants on blood vessels):
- Sorbic acid and benzoic acid in eye solutions and foods
- Cinnamic aldehyde in cosmetics
- Histamine, acetylcholine and serotonin in nettle stings

3. Urticarial vasculitis:

Type III hypersensitivity, cutaneous small vessel vasculitis with pronounced C5a-mediated mast cell degeneration

4. Idiopathic:

Many forms of physical urticarias

Basic Pathomechanism (Mast Cell Dependent)

The Mast Cell

The cutaneous mast cells have been implicated as major 'effector' cells which, on activation, liberate mediators, resulting in vasodilatation by increase in the local permeability of capillaries and venules. Both the phenotypes of mast cells (MCTC, mast cells of the skin and intestinal mucosa containing tryptase and chymase; and MCT, mast cells of the bowel mucosa, alveolar wall and nasal mucosa containing only tryptase) usually express high affinity IgE receptors (FcåRI) on their cell surface and are able to take part in IgE-dependent allergic reactions.

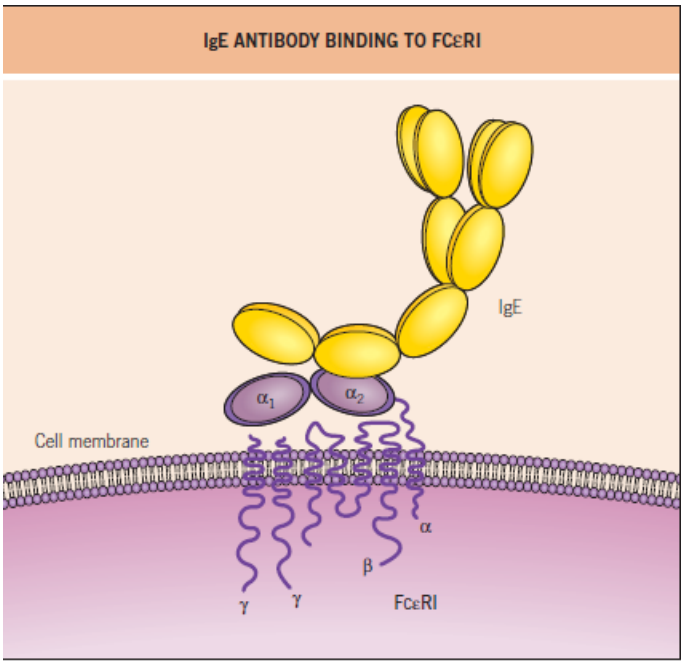


Fig 2. Mast Cell Dependent Mechanism

Degranulation

Initiation of degranulation of mast cells takes place on immunologic and non-immunologic stimuli. Immunologic degranulating stimuli bring about:

(a) binding of allergen to two adjacent receptor-bound specific IgE

(b) binding of anti- IgE autoantibodies to receptor-bound IgE, and

(c) binding of anti-FcRI autoantibodies directly to the subunits of the high affinity IgE receptor (FcRI).

Non-immunologic stimuli cause mast cell degranulation by binding to the respective, specific cell surface receptors without involving FcRI. Degranulation usually takes place either by extrusion of entire granules outside the cell or by disintegration intracellularly.

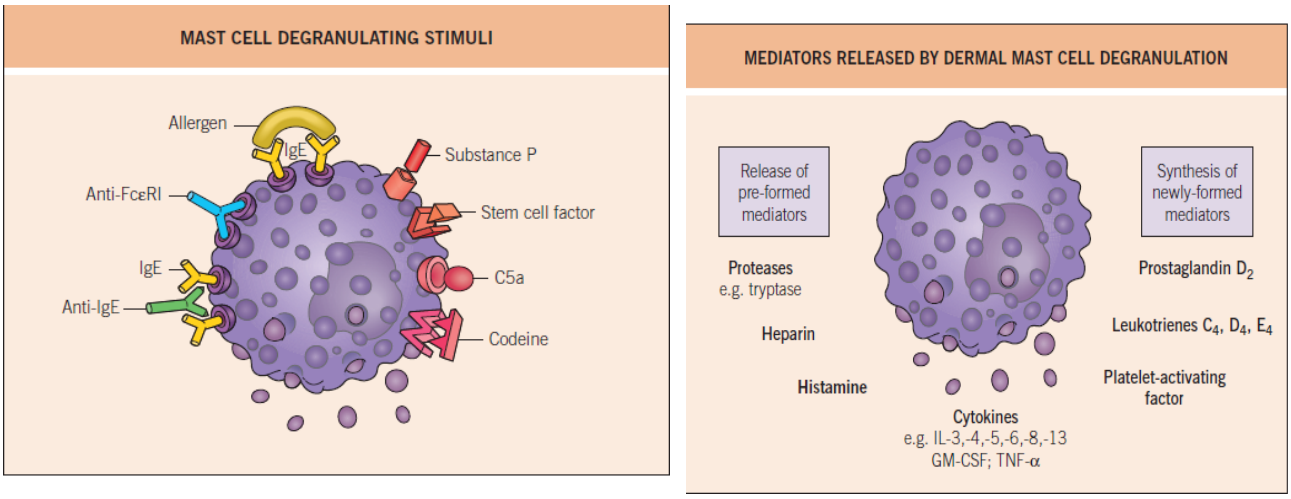


Fig 3. Mast Cell Dependent Mechanism - - Degranulation

Humoral Factors – Autoantibodies

Histamine-releasing functional IgE autoantibodies from mast cells and basophils and antibodies against the Fc portion of IgE may initiate complement activation with generation of C5a anaphylotoxin, further enhancing degranulation.

Mediators

The mast cells contain both preformed mediators (histamine, heparin, proteases like tryptase, chymase) and newly formed mediators [leukotrienes C4, D4, E4 (LTC4, -D4, -E4), platelet activating factor and prostaglandin D2]. Cytokines [tumor necrosis factor (TNF-α), interleukins (IL-3, -4, -5, -6, -8, and -13) and granulocyte– macrophage-colony stimulating factor (GM-CSF)] have also been demonstrated in human mast cells. Histamine is the most important preformed mediator. On stimulation, H1 receptors in the skin induce itching, flare, erythema and wheal, but H2 receptors contribute only to erythema and wheal. However, wheal resolution is poorly understood. Chymase and tryptase help in the

cleavage of C3 to C3a and C3b, which in turn activate mast cells and the alternative complement pathway respectively. Though convincing evidence of a significant role of PGD2 and LT4 in urticaria is lacking, they may contribute to the subsequent inflammatory events. PGE2 has been found to be an inhibitor of degranulation and thus may have a protective role in urticaria. Stimulation of FcRI upregulates the synthesis and secretion of the cytokines mentioned above. Release of TNF-α induces expression of adhesion molecules, such as E-selectin, on the endothelial cells of post-capillary venules.

Leukocytes

Basophils are greatly reduced in the presence of histamine and releasing factors in serum and they release less histamine on anti-IgE stimulation. Expression of FcRI, release of histamine, IL-4, IL-13, and LTC4 are also seen on basophilic activation. Eosinophils play a role in the persistence of wheals by generating LTC4, LTD4 and LTE4 and by releasing major basic protein (MBP). Neutrophils and lymphocytes may also enhance and perpetuate the wheal response.

Blood Vessels

Histamine and other mediators, bind to receptors on post-capillary venules, causing vasodilatation, edema and increase permeability to plasma proteins like albumin and immunoglobulin. The outcome of these events manifests clinically as a ‘wheal’. The expression of adhesion molecules on the endothelial cells of post-capillary venules results in rolling of blood leukocyte and attachment to the endothelial luminal membrane. Blood leukocytes leave the circulation and enter

the cutaneous milieu.

Other Pathomechanisms (Mast Cell Independent)

There are also other recognized patterns of urticaria where the mechanisms are not mast cell dependent. CI esterase inhibitor deficiency urticarias are, for example, complement and kinin dependent. Mast cell-independent urticarias again can be triggered by either immunologic or non-immunologic stimuli. The exact pathogenesis is not known in many patients (e.g. patients suffering from many physical urticarias).

2.6 Clinical Classification

Clinical classification of urticaria [21]

- Ordinary urticaria

  Acute

  Episodic (acute and chronic intermittent)

  Chronic (previously qualified as 'idiopathic' prior to recognition of the autoimmune subtype)
- Physical and cholinergic urticarias
- Urticarial vasculitis
- Contact urticaria
- Angio-oedema without weals
- Other syndromes resembling urticaria or angio-oedema, or with urticaria as a component

‘Ordinary’ Urticaria

All urticarias can be grouped under ‘ordinary’ unless there is a predominantly physical trigger, histopathological evidence of vasculitis or a contact factor.

Acute urticaria [22-26]

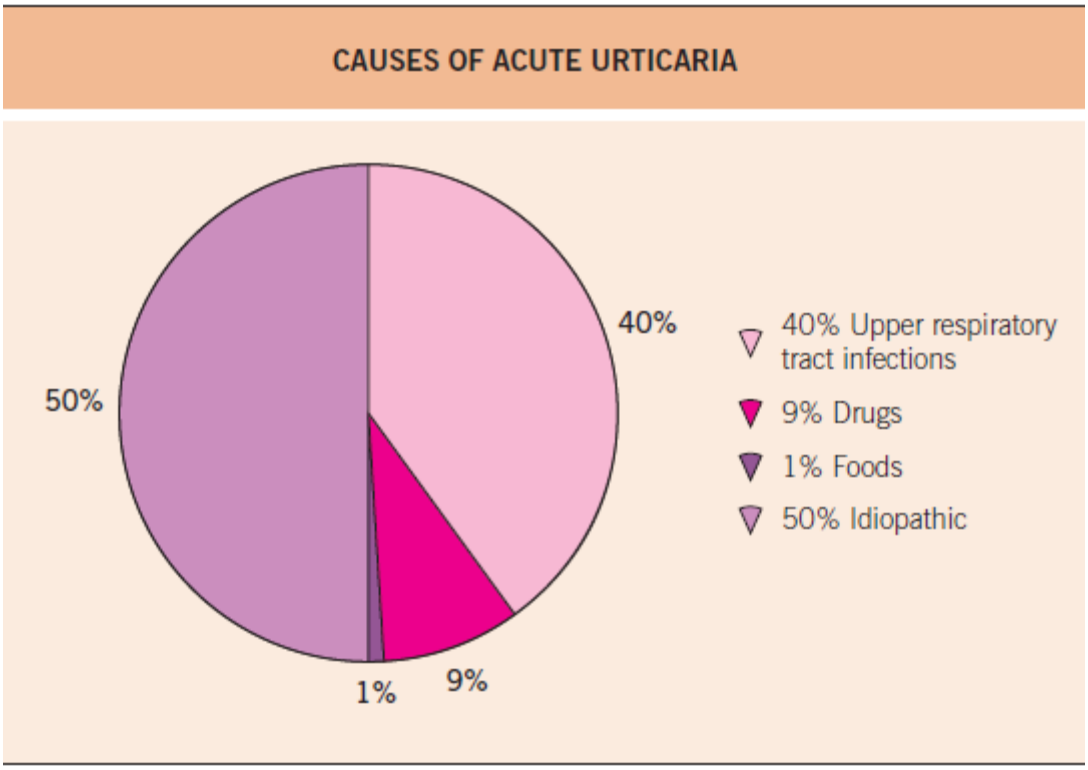


Fig 4. Distribution of causative factors for acute urticaria

- Idiopathic
- Infectious

  Upper respiratory tract infection (NOS)

  Streptococcal infection

  Hepatitis B infection

- Allergy (immediate hypersensitivity)
    - Foods
    - Drugs
    - (Inhalants)
- Non-allergic
    - Histamine liberators (e.g. codeine, atracurium)
    - Pseudoallergens & Radiocontrast media

Idiopathic

This form of acute urticaria, in which no cause can be identified, was found in more than 50% of patients with acute urticaria

Allergic

Allergic urticaria due to drugs are common, usually occurring within 36 h of drug administration. Antibiotics, especially penicillins and cephalosporins, are common causes. Increased risk factors include previous exposure and reaction to the drug or a chemically related drug, intermittent and multiple drug therapy, and a familial predisposition.

Acute urticarial reactions to food are believed to be common .Reactions typically occur within minutes and no more than 30 min. Stinging insects- bees and wasps can also cause urticarial reaction. Allergic reactions to injected sting venom are fatal.

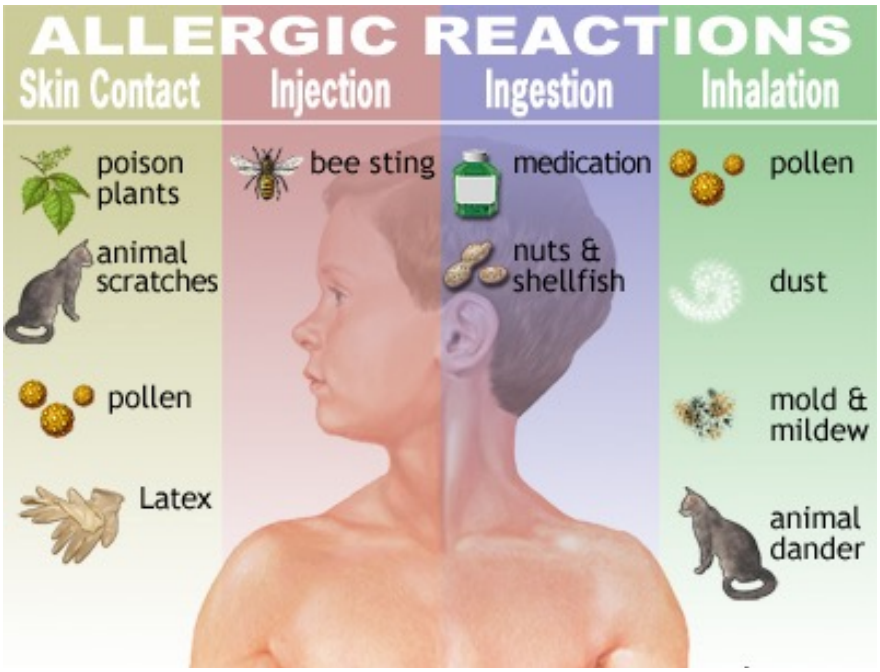


Fig 5. Causes of Allergic Urticaria

Non-allergic :

These may be due to direct histamine release from mast cells (histamine liberators) or due to other mechanisms (pseudoallergic). If they are very severe, resembling anaphylaxis, they are known as non-allergic anaphylaxis. Here, mast cell histamine release is not immunological and may occur after first exposure to a substance. Examples include morphine, codeine, atracurium and antibiotics, such as polymyxin and vancomycin. Iodine-based radiocontrast dyes may cause nonallergic anaphylaxis.

Pseudoallergic reactions :

In these patients, a reaction occurs which is not specific for a particular substance, and the same reaction can occur other substances too in the same patient. How severe a reaction the patient experiences depends on the dose of the compound causing the reaction.

NSAID's and aspirin are among the frequently implicated drugs. These cause the reactions by pharmacological mechanisms thought to be related to their activity in inhibiting the cyclo-oxygenase (COX-1) pathway of arachidonic acid metabolism, diverting it to the pro-inflammatory lipoxygenase pathway products LTC4,D4,E4 and by reducing PGE2, which is inhibitory for immunological mast cell degranulation.

Alcoholic beverages can aggravate urticaria non-specifically. White wines are often treated with sulphites, which have rarely been reported to cause urticaria and anaphylaxis. Some red wines contain measurable concentrations of vasoactive amines including histamine which could aggravate urticaria. Food may also contain vasoactive amines including histamine (such as cheese, fish, meat, tomatoes, pineapple and avocados) or histamine-releasing substances (such as in strawberries).

Infections :

Urticaria may follow non-specific viral infections, Epstein– Barr or acute hepatitis B viral infections, anisakiasis, streptococcal throat infections in children and Campylobacter jejuni.

Inhalants :

Grass pollens, mould spores, animal danders and house dust mite have been implicated as triggers of acute or chronic urticaria.

Chronic urticaria [27-33]

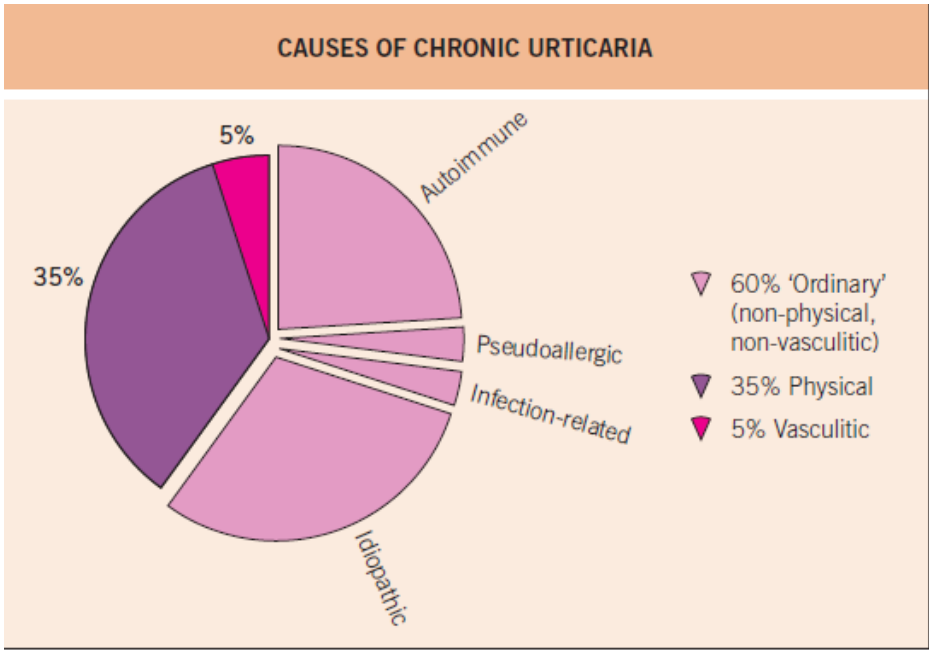


Fig 6. Distribution of causative factors for chronic urticaria

Chronic urticaria is urticaria lasting more than 6 weeks' duration

✓ Idiopathic

✓ Autoimmunity

Functional autoantibodies

✓ Pseudoallergy

Salicylates

Food colours, preservatives, antioxidants and flavour enhancers

✓ Infection

Bowel parasites

Helicobacter pylori

Candidiasis of the bowel

Idiopathic

It is still not possible to ascribe a specific aetiology to around 50% of patients presenting with the ordinary presentation of chronic urticaria.

Autoimmune

Malmros in 1946 first observed an immediate wheal and flare response when the serum of some patients with urticaria was injected in to themselves. It is only over the last decade that the autoimmune basis of urticaria has been recognized based on the presence of histamine-releasing autoantibodies and their contribution to the pathogenesis of urticaria. About 40% cases of chronic urticaria have an autoimmune basis. There are circulating anti-IgE antibodies and also antibodies to the subunit of the high affinity IgE receptor (FcRI) located on the outer surface of all mast cells and basophils in 10% and 30% patients of chronic idiopathic urticaria respectively. These autoantibodies are IgG subtypes. In autoimmune urticaria, most autoantibodies are anti-FcRI and functional antibodies bind to FcRI in the presence of IgE but hardly in its absence. The IgG subtypes of autoimmune urticaria are IgG1 and IgG3 which can fix complement. Complement is a necessary cofactor and early components of the complement cascade are activated by binding of autoantibodies to antigens (FcRI or IgE). Histamine release is augmented by binding of C5a to complement receptors on mast cells or basophils. Anti-FcRI autoantibodies are also present in healthy nonallergic individuals in a non-functional state. How these non- functional autoantibodies become pathogenic is explained by a hypothesis termed ‘conditional immunity’. Usually FcRI is

occupied by IgE and anti-FcRI cannot bind. A ‘change in receptor occupancy’ takes place when FcRI is not covered by IgE, facilitating anti-FcRI to bind to FcRI and become functional to release mediators. Thus, ‘conditional immunity’ as a unifying concept can explain the pathogenesis of urticaria by a disturbance in the receptor ligand equilibrium. Basophils have been found in a reduced number in the peripheral blood in autoimmune urticaria because of their recruitment in wheals. Mast cells, being primary effector cells, increase 10 folds in lesion. HLA-DR B1*04, HLA-DQB1*0301/4 and HLA-DQB1*03202 have been found in an increased frequency in autoimmune urticaria. However, severe continuous widespread wheals may be a clinical clue.

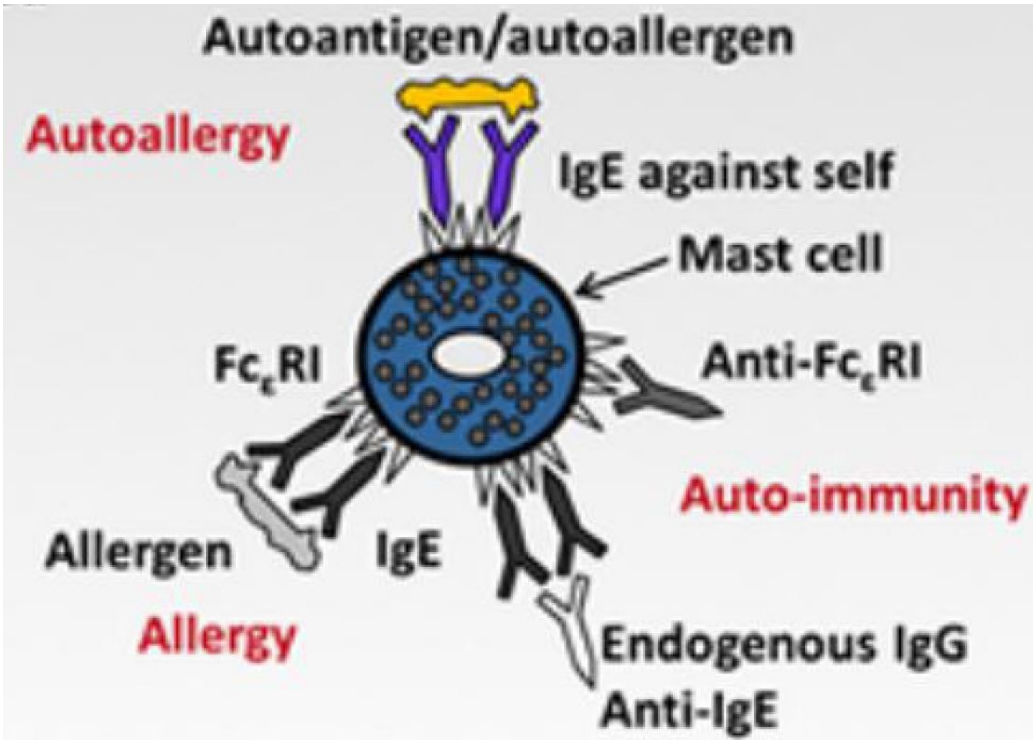


Fig 7. Various Mechanisms of Auto Immune Urticaria

Pseudoallergy

30% of chronic urticaria patients were considered to have intolerance reactions to dietary pseudoallergens as causing or aggravating their urticaria in a quality of life study. However, dietary additives and salicylates may be one of many factors that aggravate existing chronic urticaria

Infections and infestations

Bacterial infections, such as dental sepsis, sinusitis, urinary tract and gallbladder infections also cause urticaria. H. pylori infection of the stomach has been associated with chronic urticaria. Protozoa or helminthic infection in the tissue may be a cause. Linear weals may follow migration of Ancylostoma and Strongyloides worms.

Aggravating factors

Aspirin and other non-steroidal anti-infl ammatories

Dietary pseudoallergens

Upper respiratory tract infections (NOS)

Pressure

Overheating

Premenstrual period in women

Alcohol

Stress

Unrelated viral infections

Implants and nickel allergy

Physical Urticarias [34 - 55]

Physical and cholinergic urticarias

Here a specific physical stimulus induces reproducible wealing. Cholinergic urticaria occurs in response to sweating caused by an increase in core temperature. Wealing caused by physical stimuli occurs within minutes and persists for less than 30–60 mins.

A classification of physical urticarias :

- ❖ Due to mechanical force
    - Dermographism
        - Immediate
            - Symptomatic dermographism
            - Simple dermographism
        - Red dermographism
        - Cholinergic dermographism
        - Delayed dermographism
        - Associated with mastocytosis (Darier's sign)
    - Delayed pressure urticaria
    - Vibratory angio-oedema
- ❖ Due to heat
    - Generalized heating
    - Cholinergic urticaria
        - Variants

Cholinergic pruritus

Persistent cholinergic erythema

Cholinergic dermographism

Exercise-induced anaphylaxis

Localized heating : Heat contact urticaria

❖ Due to cold

Acquired

Primary (idiopathic)

Localized cooling

Cold erythema

Immediate cold contact urticaria

Delayed cold contact urticaria

Localized cold contact urticaria

Generalized

Generalized reflex cold urticaria

Cold-dependent cholinergic urticaria

Secondary (to serum cryoproteins)

❖ Others

Solar urticaria

Aquagenic urticaria

Dermographism

This involves the triple response which may arise from firm stroking of the skin - local erythema due to capillary vasodilatation, followed by oedema and a surrounding flare due to axon reflex-induced dilatation of arterioles. There is rapid appearance of a linear wheal with flare at the site where a brisk and firm stroke is made with a firm object. Immediate dermographism is classified into two major forms: simple and symptomatic. Simple immediate dermographism is seen in 5% of normal people and may be considered as an exaggerated physiological response. Symptomatic dermographism is the commonest of the physical uricarias and the patients, most frequently young adults, complain of pruritus before the wheals appear. Its prevalence in chronic idiopathic urticaria is estimated to be 22%. Symptomatic dermographism is most easily diagnosed by using a calibrated instrument, the dermographometer.

There are some special types of dermographism :

1. Delayed dermographism
2. Cholinergic dermographism
3. Cold dependent dermographism
4. Red dermographism
5. White dermographism
6. Black dermographism

Pressure Urticarias

These may be immediate or delayed.

Immediate Pressure Urticaria : Wheals occurs within minutes of applying perpendicular pressure to the skin. Urticaria persists for 30 minutes to a few hours.

Delayed Pressure Urticaria : The swelling of delayed pressure urticaria (DPU) takes place within 30 minutes to 12 hours after pressure and is often pruritic and painful, and persists for 12 to 72 hours. Lesions appear at the site of tight clothing (like the waistline), on the hands after manual work, on the buttocks after sitting on hard surfaces, or on the soles after standing (especially on a ladder). The diagnosis of DPU: keeping standardized weights on defined areas for specified times and watching for a palpable wheal locally 2 to 8 hours later.

Vibratory angio-oedema : Any vibratory stimulus such as jogging, vigorous towelling or using lawnmowers induces a localized, red, itchy swelling within minutes and lasting less than a few hours.

Urticaria Due to Temperature Changes

Cholinergic Urticaria : It is a type of urticaria characterized by the appearance of very small (1–2 mm) papules (micropapules) due to stimulation of sweating either by increased core temperature or by emotional stress. Sometimes, gustatory stimuli, such as peppery or sour foods, can precipitate an attack. The lesions first tend to appear over the neck and upper thorax. These areas appear flushed. Gradually other areas are involved and lesions become confluent, resembling angioedema. The lesions usually persist for a few minutes to an hour or two.

Occasionally, lacrimation, salivation and diarrhea are seen, indicating severe cholinergic stimulation. Systemic features like abdominal cramping, diarrhea or even fainting may be seen. Initiating typical wheals by warming [e.g. taking a hot bath (42^0C) for 15 minutes to raise the core temperature by 0.7–1^0C or simply asking the patient to exercise in a hot environment] is the best way to diagnose cholinergic urticaria.

Localized Heat Urticaria : It is an extremely rare form of physical urticaria where wheals restricted to warmed areas usually start within 2 to 15 minutes of contact with heat and last for 1 to 3 hours they may show a delayed appearance and disappearance of wheals, with even 10 hours required for complete resolution. The minimum temperature required to induce localized heat urticaria is 39^0C. Heated autologous serum at 40^0C, when injected, reproduces a similar eruptions.

Adrenergic Urticaria (Stress Induced Urticaria)

This is a rare type in which multiple small wheals are induced by stress, but not by heat and exercise. It is differentiated clinically from cholinergic urticaria by the presence of blanching and vasoconstriction surrounding the wheals. It can be reproduced by intradermal injections of epinephrine and norepinephrine, but not by acetylcholine.

Cold Urticarias

Cold urticarias represent a heterogeneous group of conditions in which cold exposure leads to wheals within minutes. They can be broadly divided into:

(a) primary cold urticaria (96%), and (b) secondary cold urticaria (4%)

Exercise Induced Urticarias

In this type, exercise induces anaphylactic symptoms. It can occur without the typical wheals of cholinergic urticaria and is produced by exercise, but not by an increase in core temperature that usually provoke cholinergic urticaria. The common precipitating exercises are jogging and active sports. Itching occurs first, followed by urticaria and angioedema, which persist for 30 minutes to 4 hours

Food and Exercise Induced Anaphylaxis

This is characterized by angioedema and/or anaphylaxis occurring within minutes of exercise if it follows either prior ingestion of a specific food (e.g. wheat) or sometimes within four hours of a heavy meal. Specific foods implicated are shellfish, wheat, vegetables and fruits like grapes, apples, tomatoes and nuts.

Solar Urticaria

It is a rare condition where itching, erythema and wheals appear rapidly within minutes in areas of sun exposure and disappear within an hour after exposure ceases. SU is broadly divided into primary solar urticaria (PSU), where no other factors that can secondarily sensitize to sunlight have been detected, and secondary solar urticaria (SSU). There are also special types of SU :

Primary Solar Urticaria

Secondary Solar Urticaria

Fixed Solar Urticaria

Delayed Solar Urticaria

Aquagenic Urticaria

Characterized by the eruption of small pruritic wheals surrounded by a flare on contact with water at any temperature. The wheal disappears within 30 to 60 minutes after contact with water has ceased . All forms of water—tap, swimming pool, distilled water, high humidity, tears, sweat and saliva—induce whealing. The upper trunk and neck are usually affected in contrast to aquagenic pruritus where water-induced itching without wheals predominantly occurs on the legs and lower trunk.

Contact Urticaria

It is an immediate urticarial reaction of a local wheal and flare that appears within minutes to an hour after contact with a provoking substance. Contact urticaria can be classified into two broad groups according to its pathomechanisms: 1) non-immunologic contact urticaria (NICU), and (2) immunologic contact urticaria (ICU).

Commonly encountered contactants causing nonimmunologic contact urticaria

1. Foods: Fish, capsicum
2. Fragrance and flavoring agents: Balsam of Peru, menthol, vanilla, cinnamon
3. Drugs: Benzocaine, dimethyl sulfoxide, methyl salicylate, tar extracts, tincture of benzoin, capsaicin, camphor, chloroform
4. Plants: Nettles, chrysanthemum
5. Animals: Arthropods, caterpillars, moths
6. Preservatives and germicidals: Benzoic acid, chlorocresol, formaldehyde

7. Others: Acetic acid, benzophenone, cobalt chloride, turpentine, sulfur

Immunologic Contact Urticaria

The reaction in ICU is well explained by a type I hypersensitivity reaction (IgE mediated) in a previously sensitized person. Cross sensitization is well documented; a patient sensitized to one protein can react to another protein due to the presence of a chemically related allergen in both the proteins.

Commonly encountered contactants for immunologic contact urticaria

1. Dairy foods: Milk, egg, cheese

2. Fruits: Apple, banana, litchi, lime, mango, orange, watermelon, peanut

3. Vegetables: Beans, carrot, cabbage, cucumber, garlic, onion, tomato, soybean

4. Meat: Chicken, pork, lamb, beef

5. Drugs: Aspirin, ampicillin, bacitracin, gentamicin, neomycin, rifamycin

Fig 8. Food substances causing urticaria

Urticarial Vasculitis

Urticarial vasculitis (UV) is characterized clinically by the presence of urticarial wheals lasting more than 24 hours and histopathologically by vasculitis in the form of vessel inflammation, perivascular hemorrhage, fibrinoid necrosis and leukocytoclasis. It is a type III hypersensitivity reaction. UV is more common among middle aged women, though it occurs unusually in children.

Distinctive urticarial syndromes:

- ❖ Systemic capillary leak syndrome / Clarkson's syndrome
- ❖ Schnitzler's syndrome / Urticarial vasculitis with monoclonal gammopathy
- ❖ Cryopyrin-associated periodic syndrome / Muckle–Wells syndrome
- ❖ Familial Mediterranean fever
- ❖ Hyper-IgD syndrome
- ❖ TNF-receptor-associated periodic syndrome (TRAPS) / Familial hibernian fever

Urticaria in childhood :

Cow's-milk allergy is the commonest cause of urticaria in infants. There is less itching and a greater tendency for weals to become purpuric. Acute haemorrhagic oedema of infancy (purpura en cocarde) occurs in very young children and is borderline between urticaria and vasculitis.

Fig 9. Papular lesions seen in urticaria

Fig 10. Urticarial Vasculitis

Fig 11. Urticarial Rashes

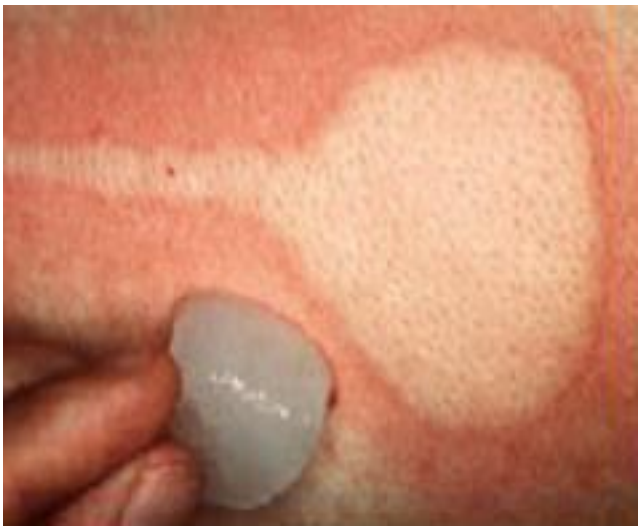


Fig 12. Cold Urticaria

Fig 13. Cholinergic Urticaria

Fig 14. Aquagenic Urticaria

Fig 15. Dermographism

2.7 Clinical Features & Investigations

Clinical Features [56-58] :

Itchy, erythematous pale to pink, oedematous, raised areas of the skin are present with a surrounding red flare. They occur anywhere on the body,in variable numbers and sizes, ranging from a few millimetres to large lesions, of varying shapes including rounded, annular, serpiginous and bizarre patterns. Very rarely, bullae may form when oedema is intense.

Weals last a few hours and resolve within 24 hr leaving the skin with a normal appearance. They are generally very itchy and Patients tend to rub rather than scratch, so excoriation marks are unusual, but occasionally bruising may result, which may be seen particularly on thighs. Weals may be more pronounced in the evenings or premenstrually. There may be associated angio-oedema in 50% of patients with ordinary urticaria. Urticaria may be associated with systemic symptoms of malaise, loss of concentration, low mood, feeling hot and cold, headache, abdominal pain or diarrhoea.

Investigations [59-64] :

Initial work up

History taking:

- ✓ Time of onset (time of day, time of year)
- ✓ Duration of urticaria (acute or chronic)

- ✓ Duration of individual lesion
- ✓ Enquiry for food, food additives, drugs, infection
- ✓ Enquiry for home and work environment
- ✓ Family history of thyroid and other autoimmune diseases
- ✓ History of atopy
- ✓ History of dental diseases

Physical examination:

- ✓ Morphology of lesion (small papules, plaques, combination of lesions, thickness of lesions)
- ✓ Distribution (localized, generalized, sun exposed skin, other sites)
- ✓ Tests for physical urticarias (stroke, exercise, ice cube test)
- ✓ Features of systemic involvement (fever, arthralgia)
- ✓ Clinical evidence of any infection (dental caries, periodontal disease, sinusitis, cystitis, vaginitis)

Laboratory work up and special tests

Initial screening tests:

CBC, DC, ESR, platelet count

LFT

T4, TSH

Urinalysis

Stool for ova and parasites

Disease-specific focused tests:

- ➢ Autoimmune Urticaria :
  - o Peripheral basophil count (to document basopenia by a sensitive assay)
  - o Functional release assays with basophils and mast cells, and
  - o Immunoassay.
  - o **Autologous Serum Skin Test (ASST) :** The specificity of ASST is about 80%. About 50%–60% of cases of chronic idiopathic urticaria show a positive ASST, which is indicated by a red wheal with a diameter 1.5 mm greater than at the control site (saline injected site) at 30 minutes when 0.05 ml autologous serum is injected intradermally. The test is positive during disease activity and not during remission. ASST is usually negative in physical urticarias and healthy controls.
- ➢ Physical urticarias
  - o Symptomatic dermographism: Dermographometer
  - o Delayed pressure urticaria: By weighted rods modified from Illig
- ➢ Cholinergic urticaria
  - o Provocation test by intradermal injection of methacholine
- ➢ Cold urticaria
  - o Ice cube test, passive transfer of cold urticaria test, serum cryoprotein estimation.
- ➢ Food and exercise induced anaphylaxis FEIA
  - o Prick test for specific IgE-dependent FEIA

➢Solar urticaria : Spectrodermograph, Solar simulator

➢Aquagenic urticaria: Wet swab test at body temperature

➢Contact urticaria: Open patch test, prick test, scratch test, use test, RAST

➢Urticarial vasculitis: C3, CH50, Skin biopsy

➢Angioedema (Hereditary): C4, C1 esterase inhibitor (functional) (Acquired): C4, C1q, C1 INH (quantitative, functional)

➢Thyroid diseases : Thyroid antibodies

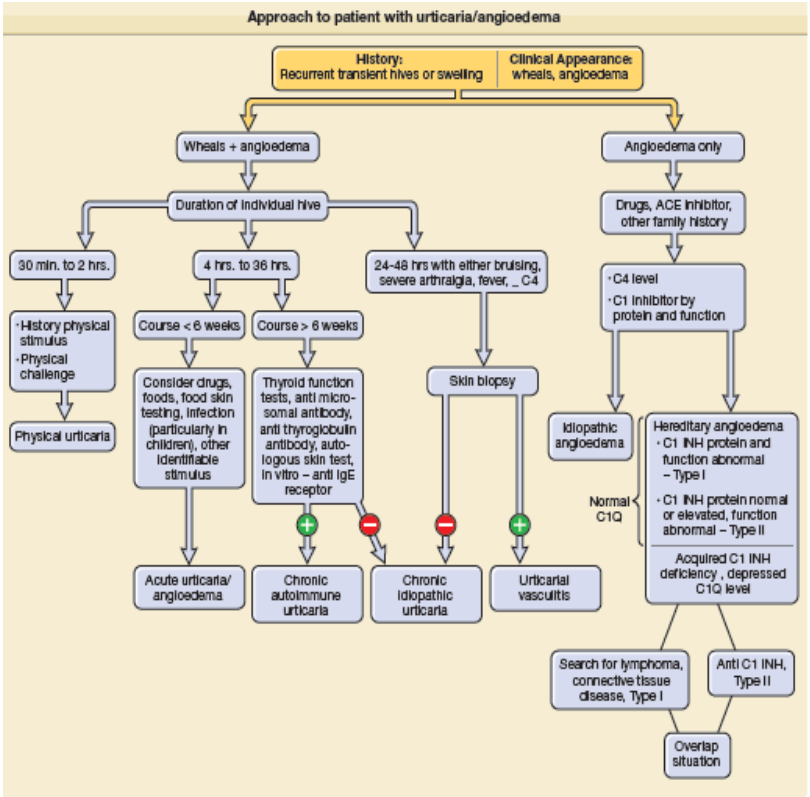
➢Hepatic diseases : Hepatitis associated antigens and antibodies

➢Collagen vascular diseases: ANA and other disease-specific tests

➢Special tests :

X-ray of the chest, sinuses, and teeth

Oral challenge test (food additives)



2.8 Differential Diagnosis

ACUTE (<6 WEEK)

- Drug reaction
  - Immunoglobulin E (IgE) mediated
  - Metabolic—idiosyncratic
  - Cellular immunity
- Food reactions
  - IgE mediated
  - Non-IgE mediated (e.g., scombroid poisoning)
- Intravenous administration
  - Blood products
  - Contrast agents
  - Intravenous γ globulin
- Infection
  - Viral in children
  - Infectious mononucleosis or hepatitis B prodrome
  - ? Bacterial in children

PHYSICAL

- Individual lesions last <2 hours
  - Cold urticaria
  - Cholinergic urticaria
  - Dermatographism
  - Local heat urticaria
  - Aquagenic urticaria
  - Cold-induced cholinergic urticaria
  - Cold-dependent dermatographism
- Lesions last >2 hours
  - Delayed pressure urticaria
  - Vibratory angioedema
  - Familial cold-induced syndromes, usually with fever

CHRONIC (>6 WEEK)

- Autoimmune, often with antithyroid antibodies
- Idiopathic
- Urticarial vasculitis
  - Idiopathic—skin only
  - Associated with other connective tissue disease
- Familial febrile syndromes with urticaria-like rash
- Schnitzler's syndrome

2.9 Management [65-103]

General Measures :

Advice and information on common precipitants should be provided to patients. Aggravating factors hinted by history (e.g. stress, alcohol, cold exposure, and heat) and the different triggers for physical urticarias should be explained to them. Clear information and advice on preventive measures (e.g. covering exposed skin in cold urticaria, and a cooling shower for cholinergic urticaria) should be provided. Avoidance of aspirin and other NSAIDs, which aggravate chronic urticarial like calamine or 1% menthol in aqueous cream may help relieve pruritus.

Acute Urticaria :

There should be an arduous attempt to identify the initiating stimulus. In most of the cases it is foods, drugs or infections. Its avoidance may help in controlling urticaria. Patients may require an oral H1 antihistamine and in resistant cases, an H2-antihistamine in addition.

If there is anaphylaxis, subcutaneous epinephrine injections with or without parenteral H1 and H2 antihistamines (e.g. 50 mg of diphenhydramine and 50 mg of ranitidine) should be given immediately. Systemic corticosteroids are sometimes useful. Measures for preventing airway obstruction, intravenous fluid replacement to combat shock and other supportive measures are to be taken as well. Pretreatment with an H1 antihistamine and corticosteroids is used in patients with an intravenous contrast media reaction and prophylactic use of corticosteroids prior to surgery is advocated in latex allergy patients.

Chronic Urticaria :

The treatment of chronic urticaria (CU) include several drugs that have antiinflammatory or immunosuppressant effects. Therapy must be individualized. The decision to use a certain medication should be specific for the patient, taking into account concomitant medical conditions and patient preferences.

Antihistaminics and other commonly used agents, which have been proven to be effective in patients, can be contiued, while starting these more advanced treatment modalities.

Terminology —

●"Antiinflammatory" - - includes agents which acts against the inflammatory cascade and has a favourable side effects profile but has less efficacy. Example - - dapsone, hydroxychloroquine and sulfasalazine.

● "Immunosuppressant" - - denotes a group of drugs that are known for their immune suppression properties but are let down by their increased prevalence of side effects. Example - - calcineurin inhibitors and mycophenolate mofetil.

First Line Therapies

Antihistamines

H1 antihistamines are the cornerstone of pharmacologic therapy in all patients of chronic urticaria. They reduce pruritus, flatten wheals, and reduce wheal duration and number.

The third generation H1-antihistamines (desloratadine, fexofenadine) are preferred over the first generation ones to start treatment as monotherapy because

they are less sedating and have less cholinergic side effects. To get consistent results these drugs are to be taken on a regular basis and not as and when required. A drug of a different pharmacological class may be used to replace the initial drug if there is no response or added to the initial agent in case of a partial response. If non-sedating antihistamines fail and if addition proves to be more cost effective than escalating the dose of the non-sedating agent, then a sedating antihistamine (first or second generation,e.g. hydroxyzine, chlorpheniramine, cetirizine or mizolastine) at night is added.

The next step is to try a combination of H1 and H2 antihistamines. The significant wheal and flare suppression by co-administered hydroxyzine and cimetidine has been documented. Doxepin, a tricyclic antidepressant, has both H1 and H2 antihistamine effects. It is effective in urticaria, with variable success rates.

As a general rule, antihistamines are safe and have few significant adverse effects. Chlorpheniramine is often selected for use in pregnancy because of its long safety record, but it is not licensed for this indication and is better avoided in the first trimester.

Second and Third Line Therapies :

These include the Anti – Inflammatory & Immunosupressant Agent along with alternative modalities like ASST and also non pharmacological therapies

Antiinflammatory agents :

The antiinflammatory agents that are best studied in chronic urticaria (CU) are dapsone, sulfasalazine, and hydroxychloroquine.

Dapsone :

Dapsone is a sulfone antimicrobial agent, well tolerated, easily available, and cost effective. In CU, dapsone acts by suppressing prostaglandin and leukotriene activity, interfering with release or function of neutrophil lysosomal enzymes, disrupting integrin-mediated neutrophil adhesiveness, inhibiting neutrophil recruitment and activation signals, and scavenging oxygen-free radical intermediates. Studies of dapsone for the treatment of CU include the following:

A case series of 11 CU patients, refractory to antihistamines alone, reported symptomatic improvement in 9 subjects within weeks of low dose of dapsone (25 mg daily). In the 2 remaining patients, the dose was titrated to 50 mg daily, which resulted in a complete response in 1 subject and partial response in the other. 7 patients had remission lasting variable periods of time after stopping the drug.

Prior to initiating dapsone therapy, CBC and liver function tests have to be checked, because this agent is avoided in a patient with anemia or abnormal liver function. Dapsone can also cause severe hemolytic anemia in patients with G6PD deficiency

In adults, starting dose is 100 mg daily. In two weeks, CBC and liver function tests are repeated and repeat these monthly for three months, and then less often. The dose can be reduced once there is a clear clinical response. A four- to six-week trial is usually sufficient to determine effectiveness.

Peripheral neuropathy, clinically significant methemoglobinemia,

agranulocytosis, and drug allergic reactions, such as the drug rash with eosinophilia and systemic symptoms (DRESS) are rare, but serious reactions that warrant immediate discontinuation of dapsone

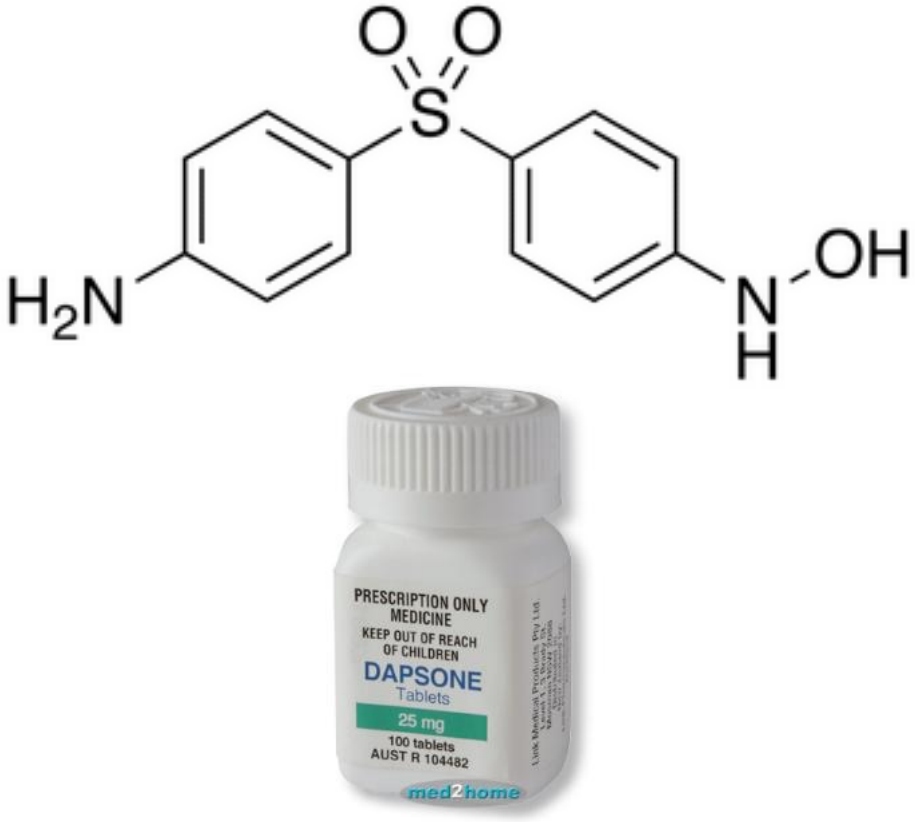


Fig 16. Biochemical Structure of Dapsone

Sulfasalazine :

Sulfasalazine is an antiinflammatory 5-aminosalicylic acid (5-ASA) derivative. Sulfasalazine is preferred for patients with underlying anemia, and therapy is initiated with the combination of sulfasalazine and hydroxychloroquine

Mechanisms of action include alteration of adenosine release, decreased leukotriene and prostaglandin synthesis, inhibition of immunoglobulin E (IgE)-

mediated mast cell degranulation, attenuation of neutrophil respiratory burst, and inhibition of early-phase events in the proliferation and differentiation of B lymphocytes

In adults, treatment is started with 500mg two times a day for a week and then can be titrated up to 1 gram twice a day. Side effects include nausea, headache, mild or transient leukopenia, and transaminitis. Laboratory monitoring with a CBC, liver function tests, and urinalysis is performed every month for the first three months, and then less often. A four- to six-week trial is usually sufficient to determine effectiveness

Hydroxychloroquine :

Hydroxychloroquine is an antiinflammatory drug and antimalarial agent. It is a relatively safe and cheap drug. The major drawback is a comparatively slower onset of action. This can be dealt with by giving hydroxychloroquine in combination with dapsone or sulfasalazine. Mechanisms of action include suppression of T lymphocyte activation and disruption of antigen processing and other cellular processes by alkalinization of intracellular vacuoles in macrophages and other antigen presenting cells

In adults, initially with dose of 200 mg twice a day. The most common adverse reactions are related to the gastrointestinal tract (nausea), skin (various macular lesions), and central nervous system (headache).Ophthalmologic problems, include corneal deposits & retinopathy are rare but possible side effects.

Corticosteroids :

One large, retrospective study reports long-term remissions in about 50% of cases of chronic urticaria with oral prednisone given in a short course in doses of 0.3-0.5 mg/kg. The prednisone was started at a dose of 25 mg/day for 3 days followed by a rapid tapering within 10 days. The remissions achieved resulted in disease control with only antihistamines at licensed doses. On administration of a second course of prednisone, the remission rate further improved.

However, systemic corticosteroids are associated with severe adverse effects on long-term treatment (glucose intolerance, hypertension, osteoporosis, gastrointestinal bleeding, and weight gain). Thus, oral corticosteroids are recommended for use only as short courses in the management of urticaria.

In another study from India, Oral Mini Pulse (OMP) therapy was used in a series of 10 patients of chronic urticaria. Over a period of 2 months, methyl prednisolone 16 mg tablets twice a week, on Saturday and Sunday, were given along with levocetirizine 5 mg tablet daily. A significant reduction in Mean Urticaria Activity Scores was observed in most patients, with only two patients reporting steroid-related side-effects. The OMP regimen may help to minimize side-effects of oral corticosteroid therapy.

Leukotriene Antagonists :

Many studies have reported the efficacy of anti LTs Montelukast and Zafirlukast in Chronic Urticaria (CU). They may be especially useful in urticaria induced by food additives and/or aspirin and other NSAIDs. Pacor *et al.* reported that the combination of antiLTs and non-sedating antihistamines gives added benefit only in urticaria elicited by a known factor (food additives, aspirin, and autoimmune urticaria). They further suggest that the combination offers no added benefit in cases of chronic idiopathic urticaria. Similarly Bagenstose et al. also reported an added benefit by addition of antiLTs to cetirizine only in cases of severe autoimmune urticaria (positive autologous serum skin test). On the basis of his findings with use of antiLTs in a series 12 patients of steroid-dependent chronic urticaria and in view of their good tolerability and low cost, Asero recommends that antiLTs should be tried in all patients with unremitting, steroid-dependent chronic urticaria before more challenging therapies are considered. A few studies in the literature have reported no benefit with antiLTs, including a study from India which reports no improvement of symptoms in chronic idiopathic urticaria patients with montelukast monotherapy.

However, a short trial with these agents may be recommended in all patients with refractory urticaria, before considering other therapeutic agents. Montelukast can be used in doses of 10 mg/day.

IMMUNOSUPPRESSANT AGENTS :

In patients who are steroid dependent and suffering from toxicity, immunosuppressants may be effective. Agents used in the treatment of chronic urticaria (CU) include cyclosporine, tacrolimus, sirolimus, and mycophenolate.

Calcineurin inhibitors :

Calcineurin inhibitors have been recommended for the management of highly symptomatic patients by experts. These drugs act by interfering with the calcium-dependent release of & responsiveness to histamine, leukotriene C4, and other mediators in mast cells and other cell types. They also have anti T lymphocyte activity. Cyclosporine also disrupts tumor necrosis factor (TNF)-alpha activity and secondarily inhibit neutrophil accumulation.

Cyclosporine :

Cyclosporine has a rapid onset (sometimes within days), a high degree of efficacy comparable with prednisone and long lasting remission.

Early studies described significant improvement with relatively high doses (5 to 6 mg per kg daily). Severe side effects are uncommon, but include hypertension and renal insufficiency.

Blood pressure, blood urea nitrogen, and creatinine should be monitored monthly and fasting lipids periodically. Serum levels may be followed to ensure that the dose is not excessive, although the optimal therapeutic level for CU has not been defined.

Tacrolimus :

Experience with the use of tacrolimus in CU is limited. In one case series, 19 patients with severe CU were treated with low-dose tacrolimus. Two patients discontinued tacrolimus due to side effects. At 12 weeks, 71 percent (12 patients) had responded to a significant degree.

Sirolimus :

Sirolimus (rapamycin) was reported to be effective in two of three patients in a case report. The patients had previously failed multiple alternative therapies including montelukast, dapsone, hydroxychloroquine, colchicine, olsalazine, and mycophenolate mofetil. Of note, sirolimus and the related agent everolimus have been implicated in causing isolated angioedema.

Mycophenolate :

Mycophenolate acts as an antimetabolite selectively for lymphocytes and also impairs expression of adhesion molecules and secondary leukocyte migration.The most common problems are gastrointestinal symptoms and leukopenia.

Choice of agent and dosing : With cyclosporine, tacrolimus, and sirolimus, a trial of one month is typically adequate to determine efficacy. Mycophenolate is slower to work and may require increasing the dose every two to four weeks to determine efficacy. Usual recommendations is to treat patients at a dose required for control of urticaria for three months, then taper the dose over several months as tolerated.

Methotrexate :

Methotrexate is an anti-metabolite used in the treatment of many chronic inflammatory diseases. It competitively inhibits dihydrofolate reductase (DHFR), an enzyme that participates in the tetrahydrofolate synthesis. DHFR catalyses the conversion of dihydrofolate to the active tetrahydrofolate. For the treatment of CU multiple mechanisms appear to be involved including: the inhibition of enzymes involved in purine metabolism, leading to accumulation of adenosine; inhibition of T cell activation and suppression of intercellular adhesion molecule expression by T cells; selective down-regulation of B cells; increasing CD95 sensitivity of activated T cells; inhibition of methyltransferase activity, leading to (de)-activation of enzyme activity relevant to immune system function and inhibition of the binding of Interleukin 1 beta to its cell surface receptor

In a report published in 2007, 3 out 4 selected cases of recalcitrant urticaria were controllable with only cetirizine after a 2 month course of Mtx (10 mg/week) given in divided doses every weekend, along with folic acid and cetirizine.

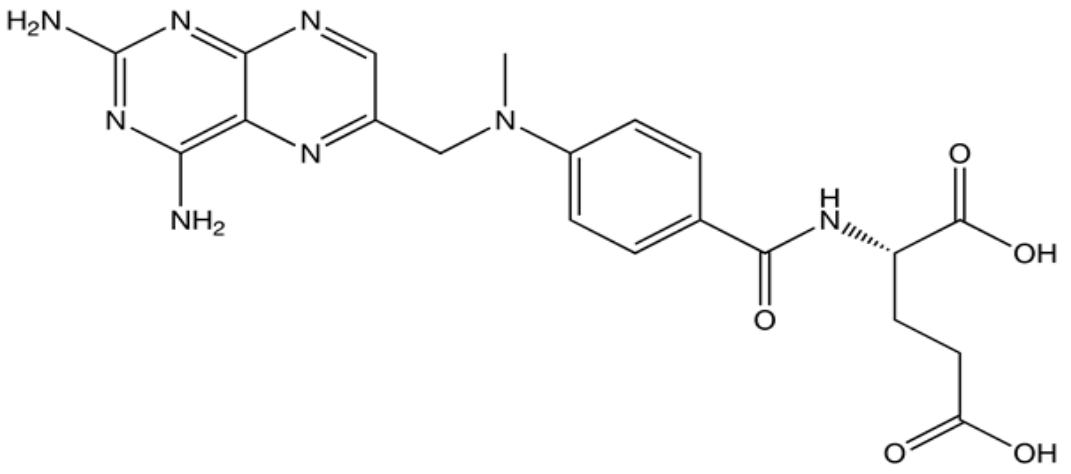


Fig 17. Biochemical structure of Methotrexate

Autologous Serum Skin Test :

A placebo-controlled trial by Staubach et al. in 2006 suggested that autologous serum skin test (ASST) positive chronic urticaria patients can benefit from autologous serum therapy.

A multicenter, prospective, open-label trial of autologous serum therapy in chronic urticaria patients from India showed its efficacy in a significant proportion of ASST-positive patients along with some ASST-negative patients as well. At least 59.7% of ASST positive and 46% ASST-negative patients showed significant improvements in signs and symptoms after nine weekly autologous serum skin injections were given. This improvement was sustained for at least 3-4 months after the last injection.

However, a randomized, three arm study from Istanbul comparing autologous serum and autologous whole blood injections to placebo injections in 88 patients of chronic urticaria could not establish a statistically significant difference in efficacy between the three methods although autohemotherapy resulted in a marked decrease in disease activity and improvement in quality of life scores in CU patients.

In another trial for autologous serum therapy from India, 20 ASST-positive patients were given weekly autologous serum injections (0.05 ml/kg/week) intramuscularly, and of those, 9 (45%) showed excellent response, while another 5 (25%) showed satisfactory response to the therapy.

In view of its low cost and good safety profile, autologous serum therapy may be a good option in ASST-positive patients with refractory urticaria.

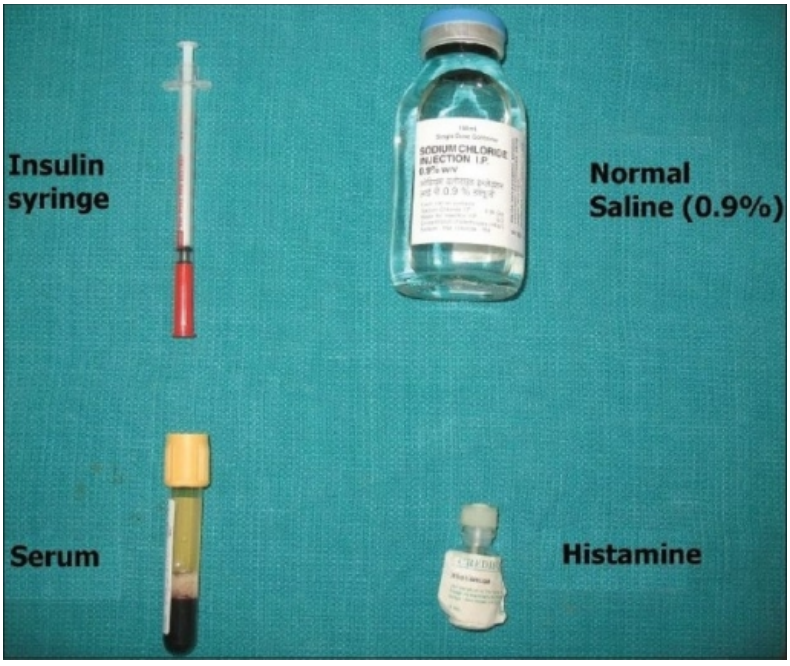


Fig 18. Autologous Serum Skin Test

Omalizumab :

Omalizumab, a monoclonal antibody directed against immunoglobulin E (IgE), is effective for chronic urticaria (CU) patients 12 years of age and older that is not controlled with H1 antihistamine therapy.

Dosing : Two doses were approved for CU refractory to H1 antihistamines: 150 mg or 300 mg every four weeks. Based upon the studies reviewed above, it is reasonable to start omalizumab with a dose of 300 mg every four weeks, and if the response is adequate, taper to a lower dose (eg, 150 mg every four weeks) or less frequent injections (every six weeks). No specific laboratory monitoring is required for patients receiving omalizumab for CU

Therapies with significant limitations **:** There are additional agents that can be useful in the management of chronic urticaria (CU), although each has limitations, including one or more of the following:

●High cost combined with limited evidence of benefit (eg, immune globulin)

●Limited evidence of benefit (eg, colchicine, methylxanthines, phototherapy)

●The potential for serious adverse effects (eg, cyclophosphamide, antifibrinolytics, anticoagulants, androgens)

●Inconvenience/intensive monitoring requirements (eg, plasmapheresis)

Immune globulin :

Immune globulin is an immunomodulatory agent that alters cell adhesion, immunoregulatory molecules, complement function, cytokine levels, autoantibody production, and anti-idiotypic networks. It can be administered intravenously (intravenous immune globulin [IVIG]) or subcutaneously (subcutaneous immune globulin [SCIG]) Adverse effects are generally predictable and manageable

TNF-inhibitors :

Tumor necrosis factor (TNF)-alpha has been shown to be upregulated in the epidermis in lesional and nonlesional skin of CU patients, but not controls. TNF-inhibitors, including etanercept, adalimumab, and infliximab, have been studied in the treatment of CU. Reports of effectiveness are limited. TNF-inhibitors have several adverse effects including injection-site or infusion-related reactions, infectious complications, and others

Colchicine :

Colchicine may act to relieve CU by suppressing leukotriene generation or by decreasing leukocyte adhesiveness and migration. The single available randomized-controlled trial evaluated 12 patients with delayed pressure urticaria, and failed to demonstrate any effect compared with placebo.

Androgens :

Androgens, which are effective in the treatment of hereditary angioedema, have been studied in chronic idiopathic urticaria and angioedema. Short-term adverse effects were reported as "infrequent," with two patients having transient elevations in transaminases that normalized without treatment cessation. The long-term adverse effects of androgens include hypercholesterolemia, hypertension, acne, mood disorders, and transaminitis, and monitoring is recommended.

Cyclophosphamide :

Cyclophosphamide are suggested for chronic urticaria patients in patients who are found to be resistant to the other treatment modalities. Its role in autoimmune urticaria has been documented based on its activity on plasma cells. Cyclophosphamide use is limited by expense, inconvenience, need for monitoring, and risk of serious adverse effects like delayed secondary neoplasia and hemorrhagic cystitis.

Antifibrinolytics and anticoagulants :

Anti fibrinolytic agents like tranexemic acid and apportion which were used to manage angioedema was tried for urticarial patients in the seventies. The basis

behind these trials was that the pathways for fibrinolysis and coagulation are similar and have common points. The anticoagulants like heparin, warfarin have also been reportedly studied for their purported use in urticaria. Inspite of these studies its use is not suggested because any benefits is outweighed by the risks associated with them.

Nondrug therapies :

Nondrug treatments that have been studied in CU include phototherapy and plasmapheresis.

Phototherapy :

Phototherapy as a treatment modality for chronic urticaria was studied and the results pointed to their efficacy in the management of solar urtcaria and other types of physical urticarias. It acts by targeting the cells and inflammatory mediators in parts of the skin which are directly irradiated. Mast cell degranulation is also affected. Several types of phototherapy – PUVA, narrow band UV-B and UV-A have been shown to effective

Plasmapheresis :

Plasmapheresis acts by removing proteins and other products of inflammation, which serve the function of immune modulation, from the blood system of the patient. Various studies showed either complete resolution or at the least improvement in symptoms.

Role of Dietary Restrictions :

Numerous food studies have demonstrated that about 35%–40% of children with moderate to severe eczema have food allergy, and eliminating the causative food causes significant improvement in the severity and extent of eczema. But food allergy is rare in adult-onset eczema.

Allergy to egg is the most common one. Other food products include milk, soy, wheat and peanuts. So , food allergy screening tests such as skin prick tests and radioallergosorbent tests should be performed in young infants . Food challenges are more accurate; reactions may be immediate or delayed. Care should always be taken with recommendations for dietary restriction in young infants. Adequate nutrition should be maintained, and consultation with a dietitian is needed.

Role of Anti H.Pylori treatment in chronic urticaria :

The role of H. pylori infection in CU has long been investigated with controversial results. Several authors demonstrated that H. pylori eradication was associated with a remission of urticaria symptoms, suggesting the possible involvement of H. pylori in the pathogenesis of this disorder. After anti-H. pylori therapy, 80% CU patients positive for H. pylori experienced complete remission of urticarial symptoms. However, Shakouri et al. utilized the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to evaluate 10 trials on the effectiveness of H. pylori eradication on CU and found that the benefit of HP eradication in patients with CU is weak and conflicting. A study in Germany showed no evidence stating that eradication of H. pylori

improves the outcome in patients with CU. Another recent study even showed that CU can be triggered by eradication of H. pylori, but the pathogenetic mechanisms are far from being clear.

Management of chronic urticaria in special populations :

Children :

Recent guidelines have strongly recommended use of modern second generation H1 antihistamines as first-line therapy for urticaria in children. In children, the same first-line treatment and weight adjusted up dosing is recommended as in adults.

There is one report of a single open label trial on use of cyclosporine in children with CIU. Seven children, aged 9 to 16 yrs, were given cyclosporine 3 mg/kg/day in two divided doses, with monitoring of serum cyclosporine levels, BUN, serum creatinine, and blood pressure. All the patients had cessation of symptoms after about 1-4 weeks and maximum by 8 weeks. No adverse effects were recorded in these seven patients.

Hepatic, renal disease :

Drug	Liver metabolism	Dose adjustment
Fexofenadine	<8%	Kidney failure
Levocetirizine	<15%	Liver and kidney failure
Desloratadine	Yes	Liver and kidney failure
Rupatadine	Yes	Liver and kidney failure
Cetirizine	<40%	Liver and kidney failure
Loratadine	Yes	Liver and kidney failure

Pregnancy and lactation :

There have been no reports of birth defects in women having used modern second-generation antihistamines during pregnancy. The latest guidelines suggest use of loratadine, cetirizine, and levocetirizine during pregnancy. These are also pregnancy category B. All antihistamines are secreted in breast milk and use of first-generation antihistamines is discouraged during lactation to avoid excessive sedation. A short course of oral corticosteroids may be considered during pregnancy in case of severe exacerbations of urticaria. Potential side effects include malformations, neonatal adrenal insufficiency, and low birth weight. Risk to benefit ratio must be assessed before administration. Although oral steroids are secreted in breast milk, they are generally considered to be safe during lactation.

Aims & Objectives

AIM OF THE STUDY

1. To compare the efficacy of treatment of dapsone, methotrexate and ASST (Autologous Serum Skin Therapy) for chronic urticaria.
2. To determine the prevalence of auto immune urticaria in patients with chronic urticaria.
3. To determine the remission rates for each treatment
4. To assess the improvement in UAS (Urticaria Activity Score) & DLQI (Dermatology Life Quality Index) with treatment.

Materials and Methods

MATERIALS AND METHODS

3.1 Type of study : Prospective, Observational & Comparative study

3.2 Study approval : Prior to commencement of this study - Thesis & Ethical Committee of Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai had approved the thesis protocol.

3.3 Place of study : Rajiv Gandhi Government General Hospital

3.4 Period of study : Duration starting from 01 Oct 2014 to 31 July 2015

3.5 Sample size : 120 cases

3.6 Selection of patients:

a) Inclusion criteria-

a) Patients with Chronic Urticaria defined as urticarial eruption of more than 6 weeks duration characterized by hives or wheals

b) Age > 18 yrs

c) Patient is resistant to treatment with anti histamines.

b) Exclusion criteria:

1. Age < 18 yrs & > 60 yrs
2. Physical urticaria / Urticaria secondary to an underlying medical condition

3. Any contraindication to the treatment modalities like pregnancy, breast feeding, women wanting to conceive or underlying medical condition
4. Has taken any treatment other than anti histamines

3.7 Study procedure:

Around 120 patients with chronic urticaria will be selected from the patients attending psoriasis out-patient clinic in Department of Dermatology, Madras Medical College. All patients will be explained about the disease, benefits & possible side effects of treatment. Informed written consent will be obtained from all patients before initiation of treatment. Detailed history will be obtained and patients will be evaluated as follows

1) General and systemic examination.

2) Dermatological examination.

3) Investigations namely complete hemogram, liver function tests, renal function tests autologous serum skin test and chest xray.

4) ENT & Dental opinion will be sought to rule out focal sepsis

The patients will be randomly allotted to any one of the following four treatment groups after calculating their Urticarial Activity Score (UAS) & Dermatology Life Quality Index (DLQI).

Group A will comprise patients who will be given oral Dapsone 50 mg for a period of 12 weeks.

Group B will comprise patients who will be given oral Methotrexate 10 mg (in 4 divided doses at 12 hourly interval) per week for a period of 12 weeks.

Group C will comprise patients who will be given Treated with ASST (Autologous Serum Skin Therapy) – 2ml of autologous serum deep intramuscular injection once a week for 9 weeks.

In addition to these, patients in all the groups will be prescribed Antihistamines.

Group D will be the control group who will receive only Antihistamines.

3.8 Follow Up Assesment :

SCREENING PROCEDURES / VISITS: Patients will be reviewed every 4 weeks at 4,8 &12 weeks for complaints and assessing clinical improvement till completion of treatment and once every two months for six months following completion

ASSESSMENT OF PARAMETERS: Blood parameters will be repeated every four weeks or as and when required and Parameters like Urticarial Activity Score(UAS) and Dermatology Life Quality Index(DLQI) will be assessed at end of treatment and at end of six months following treatment.

Patients were then divided into three categories based on these parameters into Good Responders, Average Responders & Poor Responders.

Good Responders : Patients post treatment UAS score < 2 and DLQI score $\leq$ 2

Average Responders : Patients post treatment UAS score 2 - 4 & DLQI score 2 - 9

Poor Responders : Patients post treatment UAS score > 4 and DLQI score $\geq$ 10

The higher of the two scores is taken into consideration while classifying the groups.

3.9 Variables studied:

Dependent variable: UAS & DLQI score

Independent variables:

i) Age

ii) Sex

iii) Symptoms

iv) Co-morbidities: COPD, jaundice, diabetes, obesity and malnutrition.

v) Dermatological Examination

vi) ENT & Dental Examination

vii) Blood Investigations

viii) ASST & Chest Xray

3.10 Ethical consideration

All the patients/ legal guardians were given an explanation of the study and about the investigative and operative procedures with their merits and demerits, expected results, and possible complications. If he/she agreed then the case had been selected for this study. The study did not involve any additional investigation or any significant risk. It did not cause economic burden to the patients. The study was approved by the institutional review board prior to commencement of data collection. Informed consent was taken from each patient/guardian. Data were collected by approved data collection form.

3.11 Data collection

Data were collected by pre-tested structured questionnaire. Data were collected from all the respondents by direct interview after getting informed written consent from them or from their legal guardian.

3.12 Data analysis

Data analysis was done both manually and by using computer. Calculated data were arranged in systemic manner, presented in various table and figures and statistical analysis was made to evaluate the objectives of this study with the help of Statistical Package for Social Science (SPSS).

Results

RESULTS

This prospective, observational, comparative study was carried out to determine the favourable treatment modality for patients suffering from chronic urticaria. One hundred and twenty patients with chronic urticaria were selected purposively from Department of Dermatology of Madras Medical College and Rajiv Gandhi Government General Hospital during the period of 1 October 2014 to 31 July 2015. All cases were evaluated clinically and essential investigations necessary for diagnosis were carried out. Patients initial UAS and DLQI score were calculated and recorded. Patients were then randomly divided into four groups and started on treatment with ASST, Dapsone, Methotrexate and Anti-histaminics. Patients response to treatment was followed up with UAS and DLQI score at three and six months of treatment. Based on the assessment of these scores, the response to treatment was categorised into Good, Average and Poor. All data were collected and analysed and results derived.

TABLE 1 : Age & Sex Distribution of Patients with Chronic Urticaria

Age / Sex	Male	Female	Total
18 - 29	20 (16.67)	47 (39.17)	67 (55.83)
30 - 39	6 (5)	27 (22.5)	33 (27.5)
40 - 49	3 (2.5)	11 (9.17)	14 (11.67)
50 - 59	6 (5)	0 (0)	6 (5)
Total	35 (29.17)	85 (70.83)	120 (100)

It was observed that age of 120 patients ranged from 18-56 years. Most of the patients (55.83 %) were in between 18-29 years. Females were the predominantly involved sex with male to female ration of 1 : 2.3

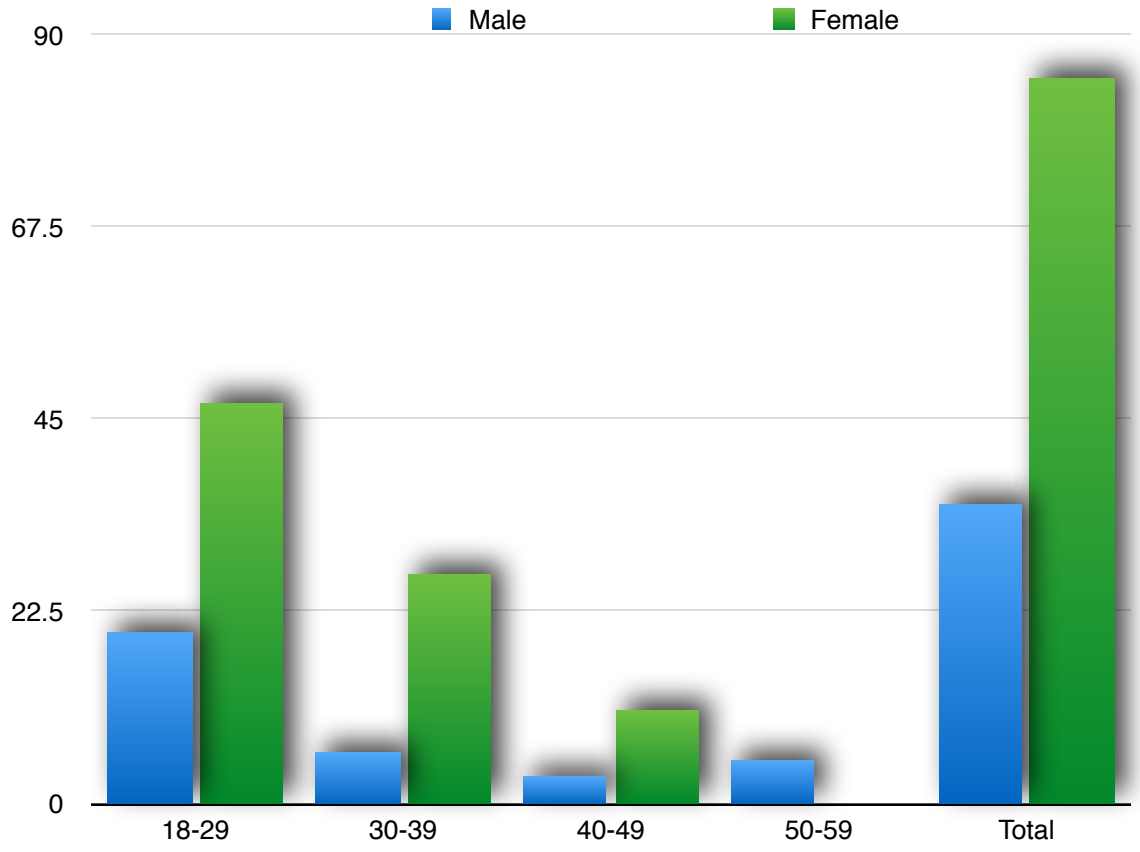


Table II : Distribution of patients on the basis of duration

Duration	No. Of Patients	Percentage
< 3 months	12	10
3 - 6 months	48	40
6 - 9 months	41	34.17
9 - 12 months	17	14.17
> 12 months	2	1.67
Total	120	100

Chronic Urticaria denotes a duration of more than 6 weeks. In our study, majority of the patients presented around 3 to 9 months, constituting nearly 75% of the total number of cases. Only two patients presented with more than a year duration.

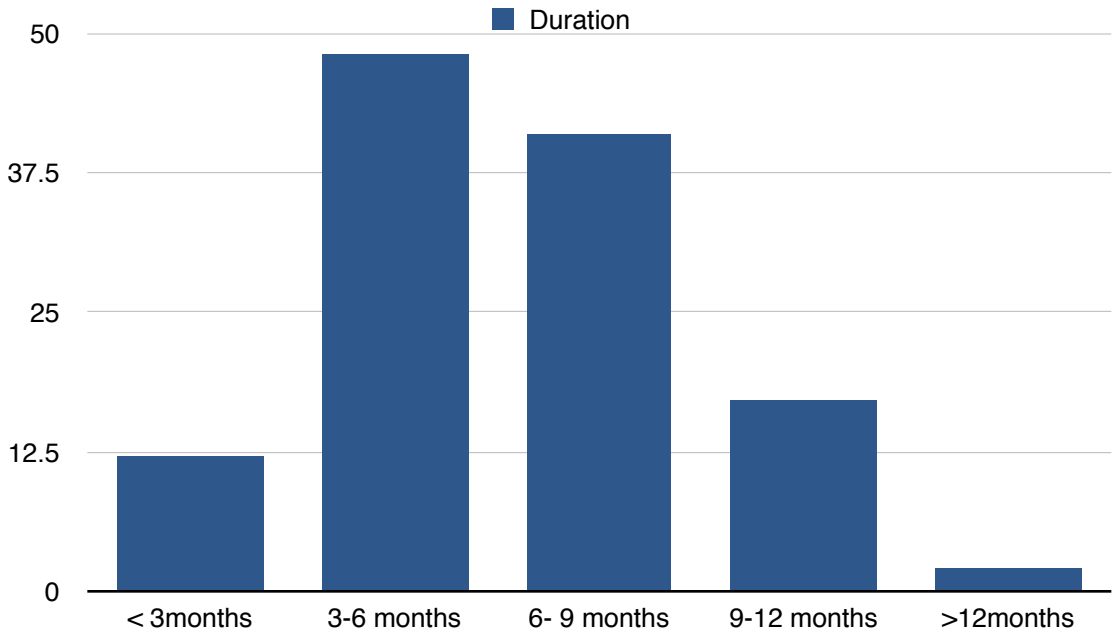


Table III: Prevalence of precipitating factors in chronic urticaria patient

Precipitating Factor	No. of Patients	Percentage
Food	18	15
Infections	12	10
Inhalant	12	10
Drugs	8	6.67
Aquagenic	4	3.33
No Specific Factor	66	55
Total	120	100

Regarding precipitating factors, food allergens were the most common precipitating factor accounting for 15% of the cases, followed by infections & inhalants like house dust seen in 10% of cases. The other precipitating factors were drugs and water related. 65 % of the total patients had no specific aggravating or trigger factor for occurrence of symptoms.

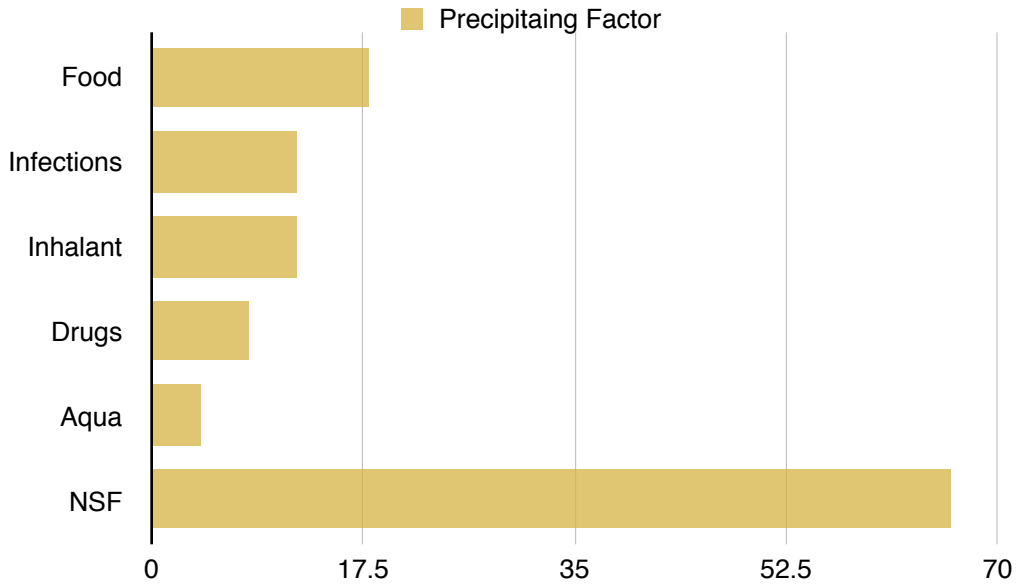


Table IV: Distribution of atopy in chronic urticaria patients

Atopy	No. of Patients	Percentage
Positive	26	21.67
Negative	94	78.33
Total	120	100

Around 26 patients (21.67%) had history or features suggestive of atopy.

TableV: Distribution of co-morbid factors in chronic urticaria patients

Co - Morbid Factor	No. of Patients	Percentage
Diabetes Mellitus	9	7.5
Systemic Hypertension	4	3.33
DM & HTN	4	3.33
BA	12	10
Hypothyroid	21	17.5
No Comorbidity	70	58.33
Total	120	100

Out of the 120 patients, 25 patients had co-existent systemic problems like diabetes mellitus seen in 9 (7.5%) patients, systemic hypertension in 4 (3.3%) patients and both hypertension and diabetes in 4 (3.3%) patients. Twenty one (17.5%) of these patients also had previously detected hypothyroidism.

Table VI : Prevalence of ASST in chronic urticaria patients

	Positive		Negative	
	Male	Female	Male	Female
ASST	7 (5.83)	37 (30.83)	28 (23.33)	48 (40)
Total	44 (36.67)		76 (63.33)	

* Figures given in parentheses are percentage value

Out of 120 patients in the study, 44 patients (36.67%) turned out to be positive for Autologous Serum Skin Test. Of these 37 patients (30.83%) were females and only 7 patients (5.83%) were males.

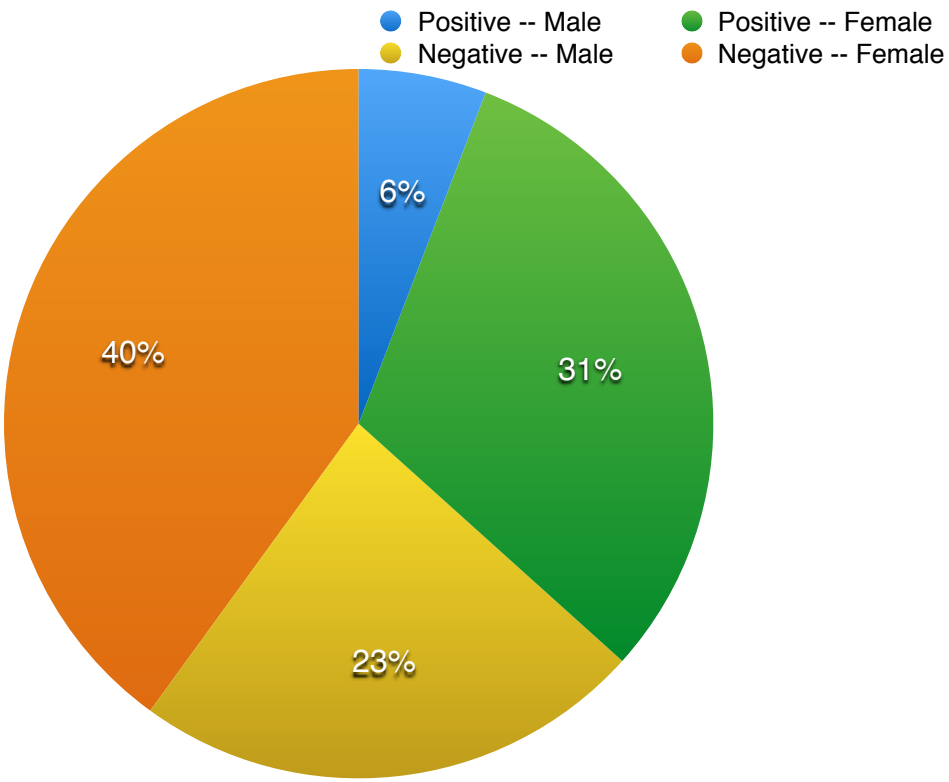


Table VII: Age and Sex Distribution based on the treatment offered

Age	ASST		Methotrexate		Dapsone		Control	
	Male	Female	Male	Female	Male	Female	Male	Female
18 - 29	5	12	5	9	7	12	3	14
30 - 39	1	8	1	7	1	8	3	4
40 - 49	-	3	1	4	1	1	1	3
50 - 59	1	-	3	-	-	-	2	-
	7	23	10	20	9	21	9	21
Total	30		30		30		30	

120 patients were divided into four groups of 30 patients each and started on respective treatment regimen. In ASST group, there were 7 males and 23 females. In methotrexate group, there were 10 male patients and 20 female patients. In dapsone group, there were nine male patients and twenty one female patients. In control group, there were nine male patients and twenty one female patients

Table VIII: Distribution of response to treatment of all four groups of patients

	Good	Average	Poor	Total
ASST	22 (73.33)	6 (20)	2 (6.67)	30
Methotrexate	10 (33.33)	14 (46.67)	6 (20)	30
Dapsone	15 (50)	13 (43.33)	2 (6.67)	30
Control	4 (13.33)	10 (33.33)	16 (53.33)	30
Total	51 (42.5)	43 (35.83)	26 (21.67)	120

* Figures given in parentheses are percentages

More than 73% of patients treated with ASST had good response to treatment while only 50% of those treated with dapsone and 33% of those treated with methotrexate had good response to treatment. Poor response was seen in 6% of ASST and Dapsone patients compared to the 20% in patients receiving Methotrexate. This is still better than the 53% with poor response in the control group.

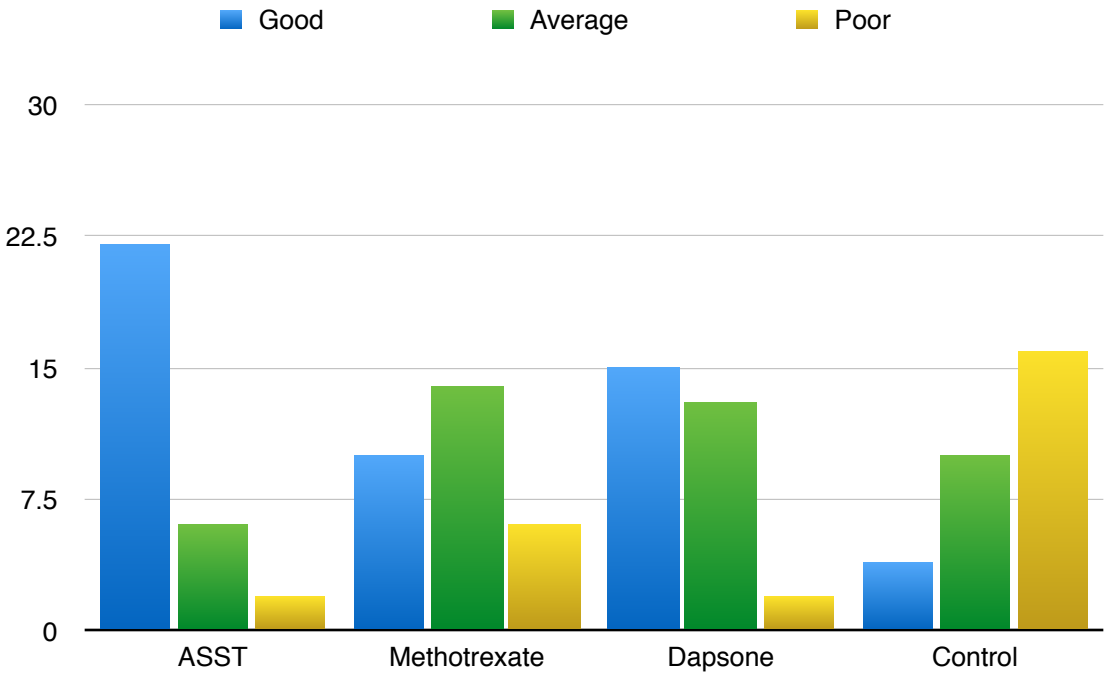


Table IX: Age & Sex Distribution of Patients with Good response to treatment

Age	ASST		Methotrexate		Dapsone		Control	
	Male	Female	Male	Female	Male	Female	Male	Female
18 - 29	3 (5)	10 (12)	0 (5)	3 (9)	5 (7)	4 (12)	0 (3)	3 (14)
30 - 39	1 (1)	6 (8)	0 (1)	4 (7)	0 (1)	6 (8)	0 (3)	1(4)
40 - 49	-	2 (3)	0 (1)	0 (4)	0 (1)	0 (1)	0 (1)	0 (3)
50 - 59	0 (1)	-	3 (3)	-	-	-	0 (2)	-
	4 (7)	18 (23)	3 (10)	7 (20)	5 (9)	10 (21)	0 (9)	4 (21)
Total	22 (30)		10 (30)		15 (30)		4 (30)	

* Figures in parentheses indicate the total number of patients in that subset

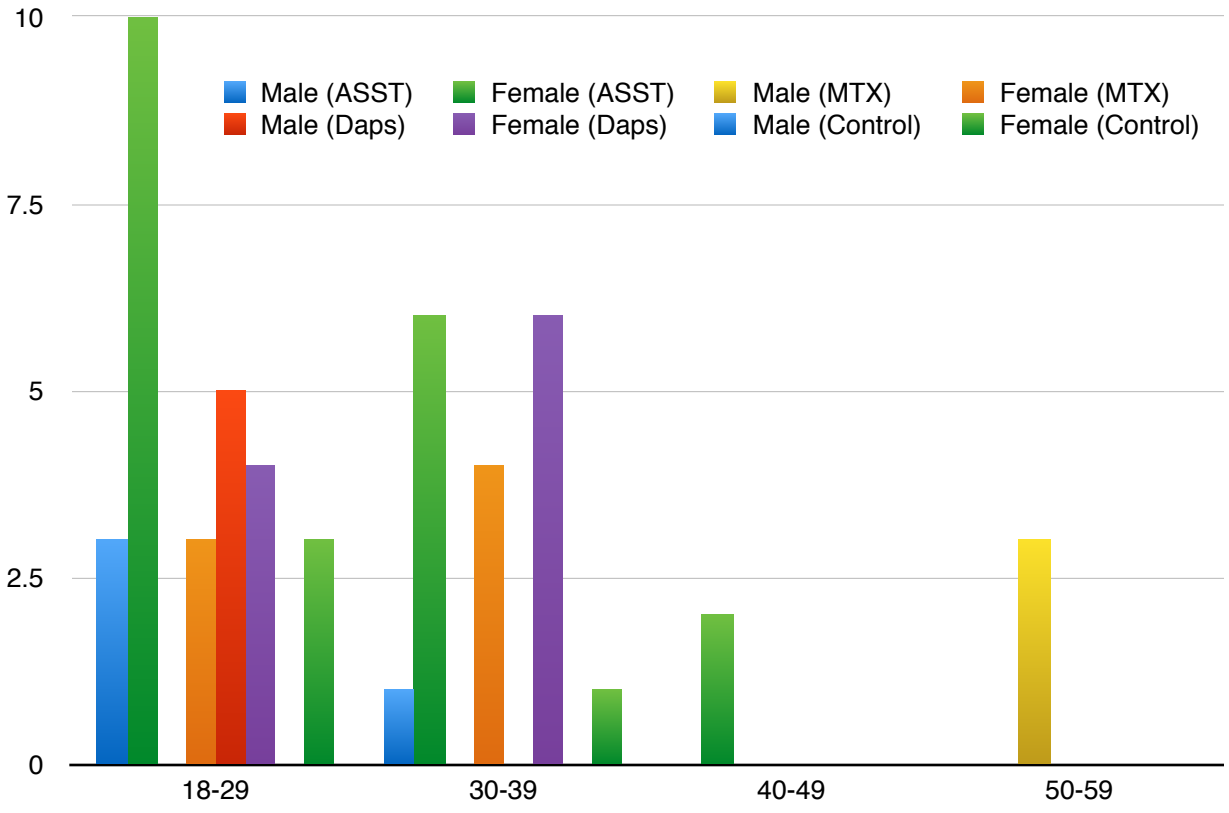


Table X: Age & Sex Distribution of Patients with Average response to treatment

Age	ASST		Methotrexate		Dapsone		Control	
	Male	Female	Male	Female	Male	Female	Male	Female
18 - 29	2 (5)	2 (12)	3 (5)	4 (9)	2 (7)	7 (12)	1 (3)	5 (14)
30 - 39	0 (1)	2 (8)	1 (1)	3 (7)	1 (1)	1 (8)	2 (3)	0 (4)
40 - 49	-	0 (3)	0 (1)	3 (4)	1 (1)	1 (1)	1 (1)	1 (3)
50 - 59	0 (1)	-	0 (3)	-	-	-	0 (2)	-
	2 (7)	4 (23)	4 (10)	10 (20)	4 (9)	9 (21)	4 (9)	6 (21)
Total	6 (30)		14 (30)		13 (30)		10 (30)	

* Figures in parentheses indicate the total number of patients in that subset

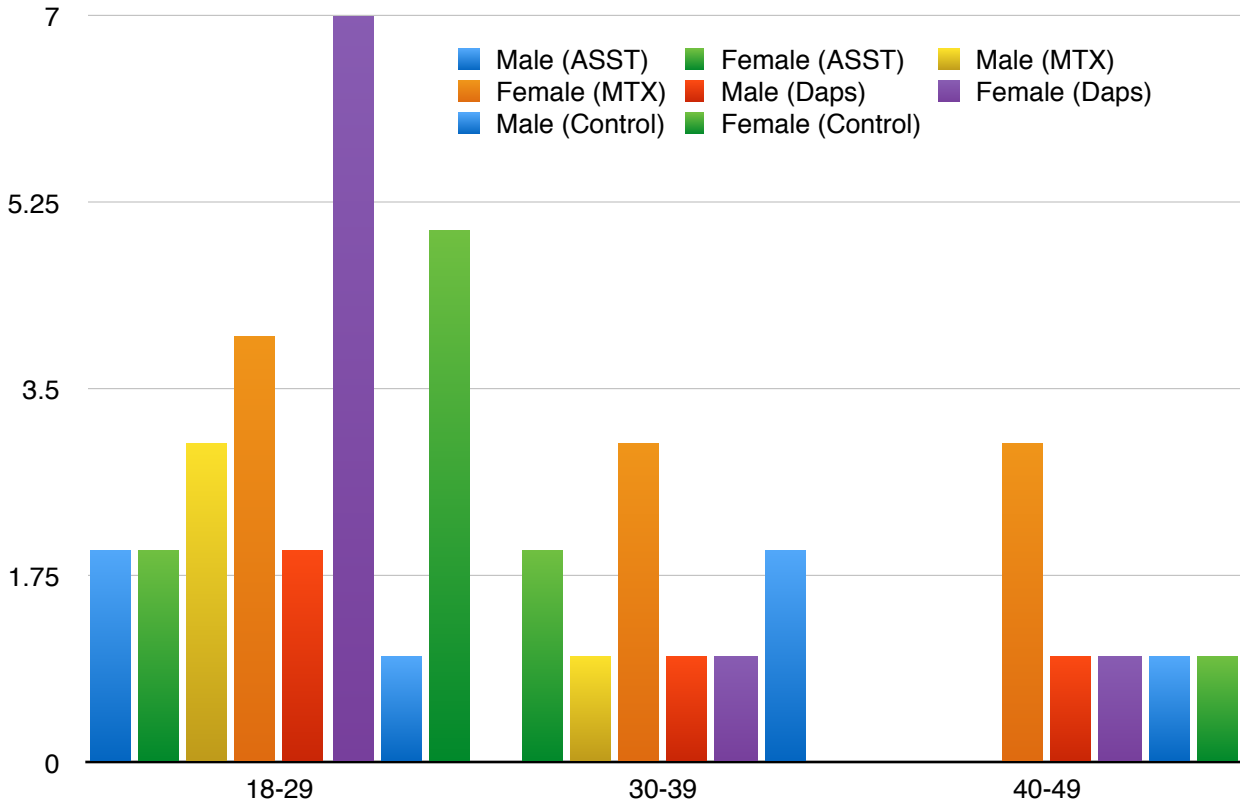


Table XI: Age & Sex Distribution of Patients with Poor response to treatment

Age	ASST		Methotrexate		Dapsone		Control	
	Male	Female	Male	Female	Male	Female	Male	Female
18 - 29	0 (5)	0 (12)	2 (5)	2 (9)	0 (7)	1 (12)	2 (3)	6 (14)
30 - 39	0 (1)	0 (8)	0 (1)	0 (7)	0 (1)	1 (8)	1 (3)	3 (4)
40 - 49	-	1 (3)	1 (1)	1 (4)	0 (1)	0 (1)	0 (1)	2 (3)
50 - 59	1 (1)	-	0 (3)	-	-	-	2 (2)	-
	1 (7)	1 (23)	3 (10)	3 (20)	0 (9)	2 (21)	5 (9)	11 (21)
Total	2 (30)		6 (30)		2 (30)		16 (30)	

* Figures in parentheses indicate the total number of patients in that subset

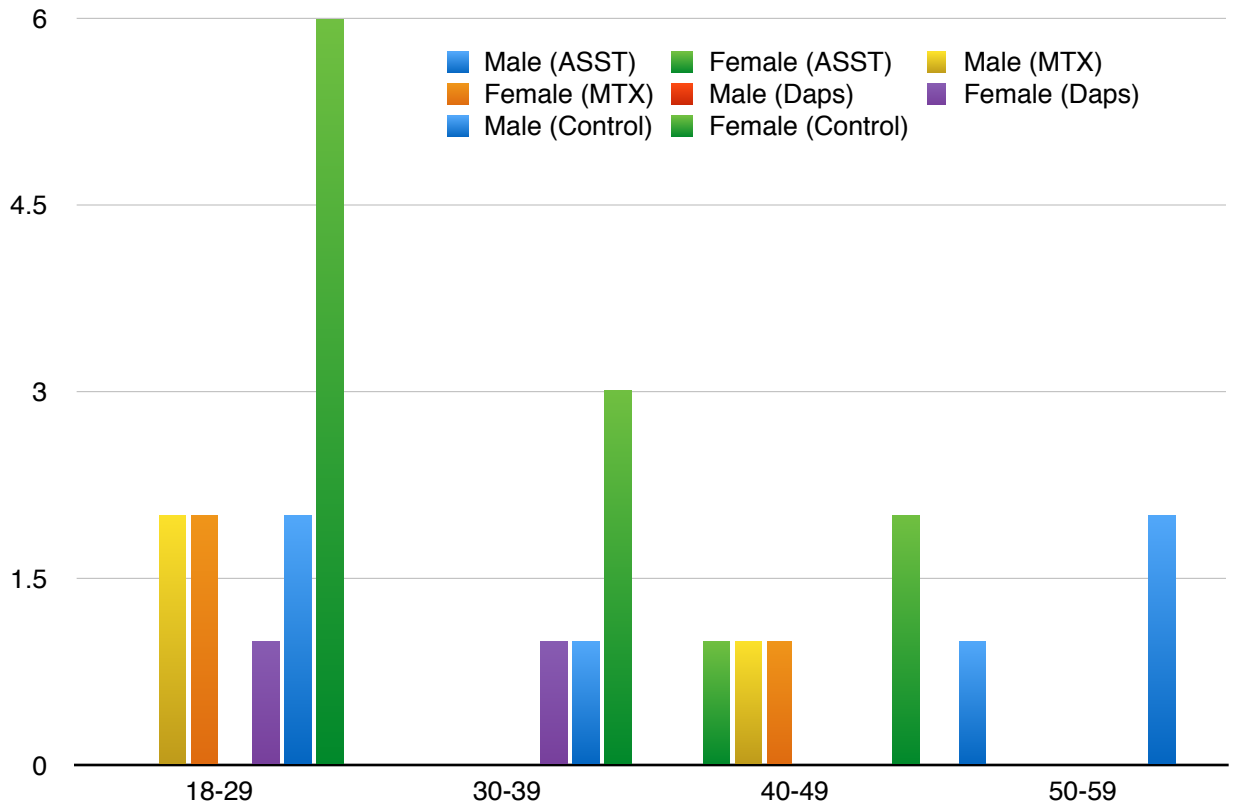


Table XII: Response to treatment in ASST positive patients

	Good	Average	Poor	Total
ASST	11 (78.57)	3 (21.43)	0	14
Methotrexate	5 (50)	4 (40)	1 (10)	10
Dapsone	4 (50)	4 (50)	0	8
Control	2 (16.67)	6 (50)	4 (33.33)	12
Total	22 (50)	17 (38.64)	5 (11.36)	44

* Figures in parentheses indicate the percentages

ASST positive patients generally had a good response to treatment with poor response seen in only five patients (11%) across all groups, with four of those patients being in the control group. Nearly eighty percent of the patients in the ASST treatment group had good response to treatment.

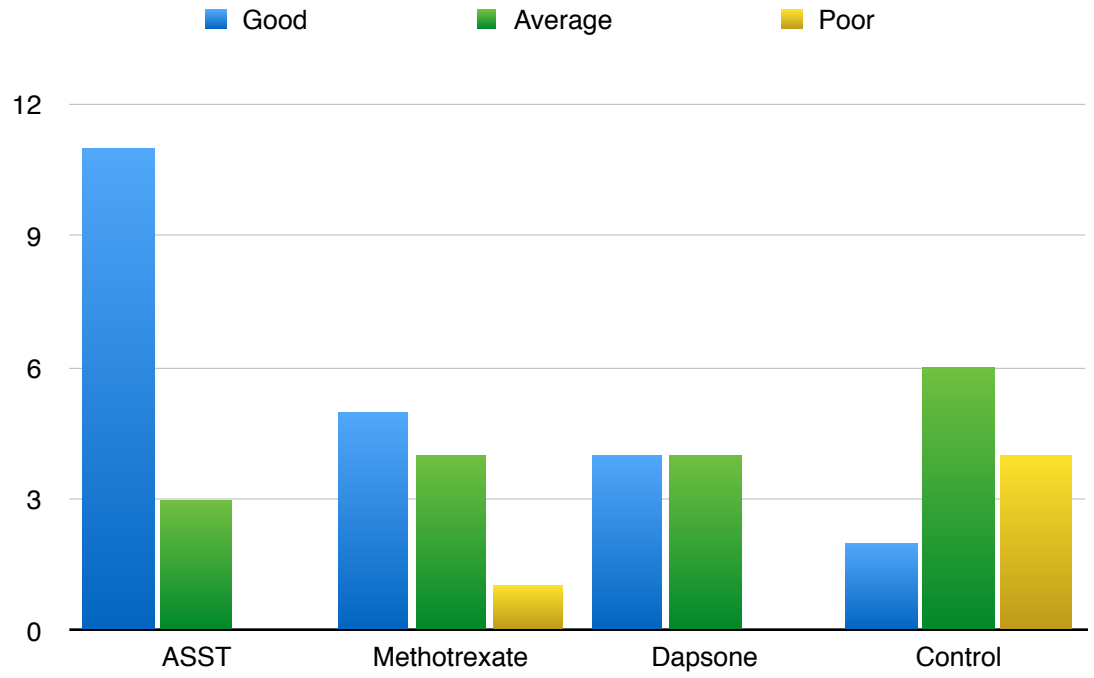
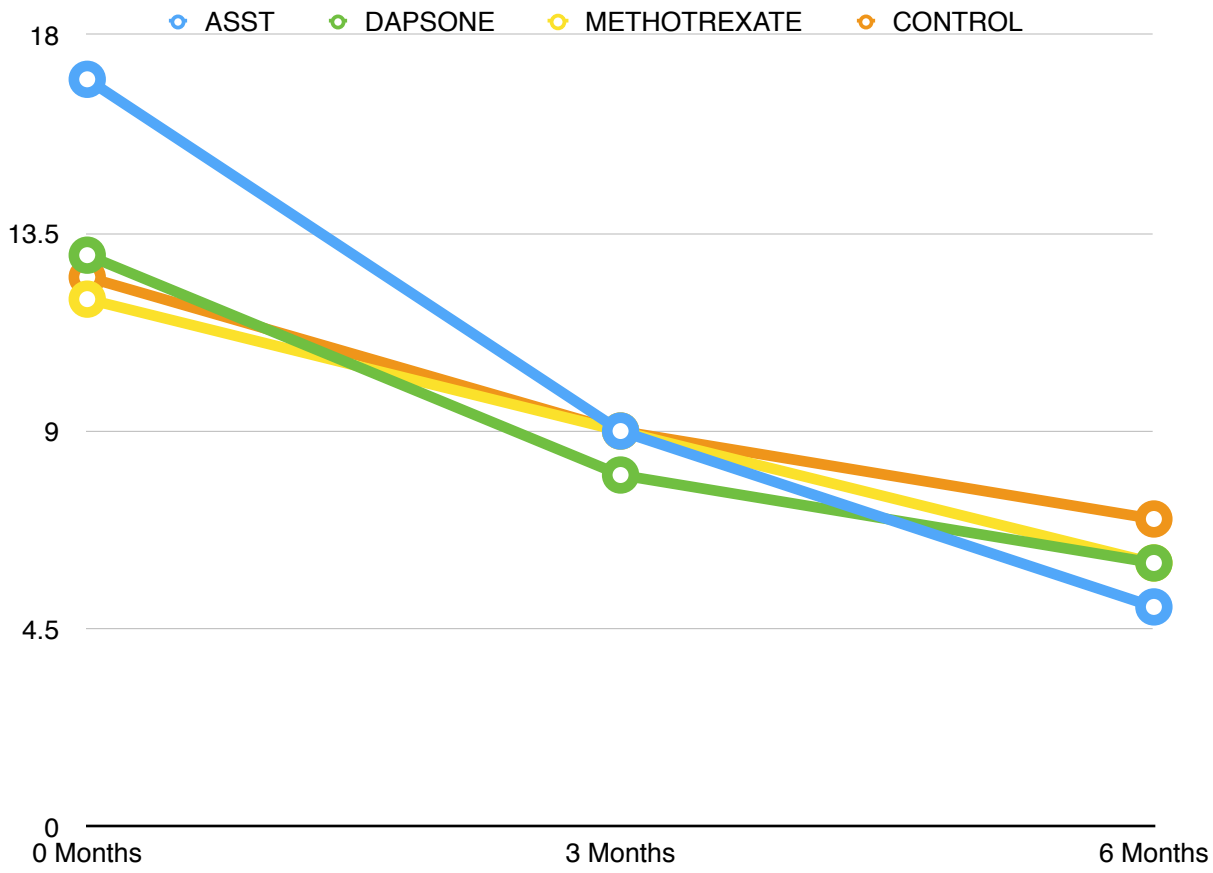
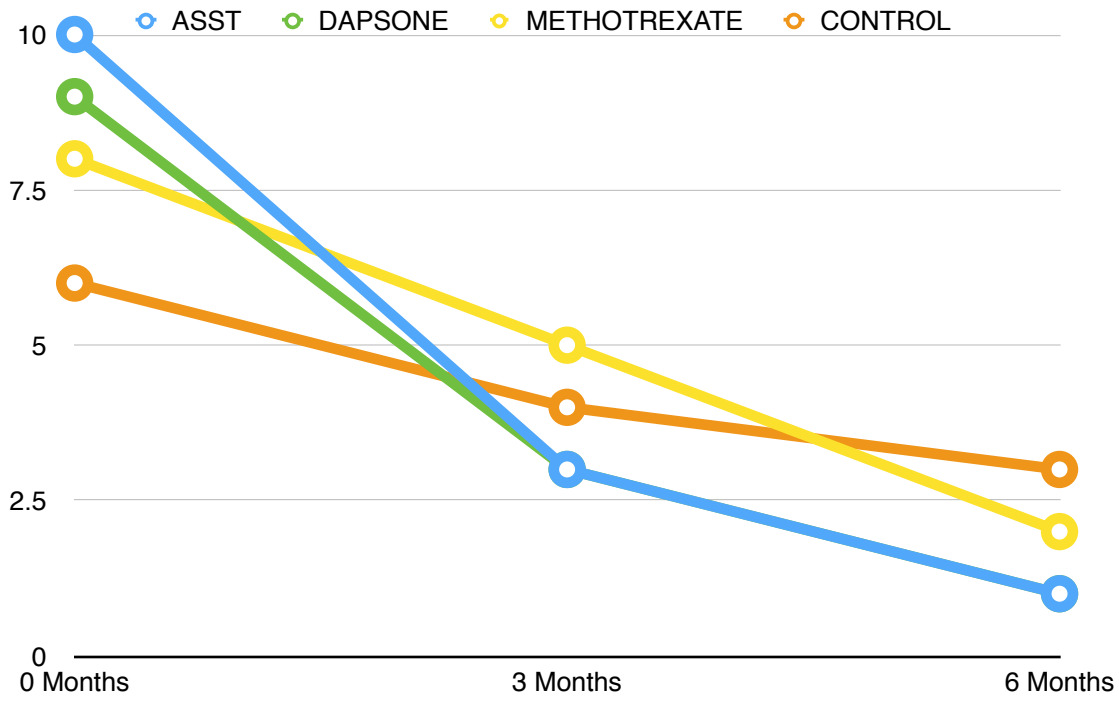


Table XIII : Average DLQI score of patients in different treatment groups

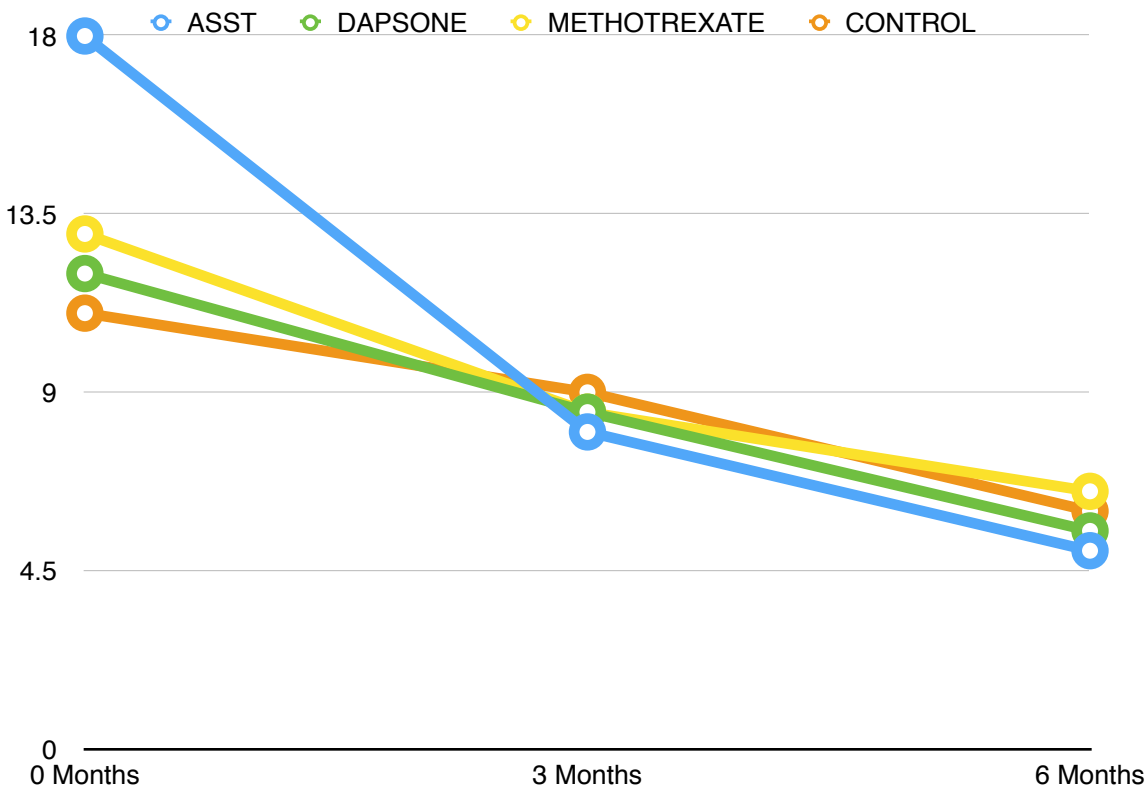
	ASST			Methotrexate			Dapsone			Control		
Months	Good	Average	Poor	Good	Average	Poor	Good	Average	Poor	Good	Average	Poor
0	10	18	22	8	13	19	9	12	18	6	11	17
3	3	8	15	5	8	14	3	8	12	4	9	14
6	1	5	8	2	6	12	1	5	10	3	6	12



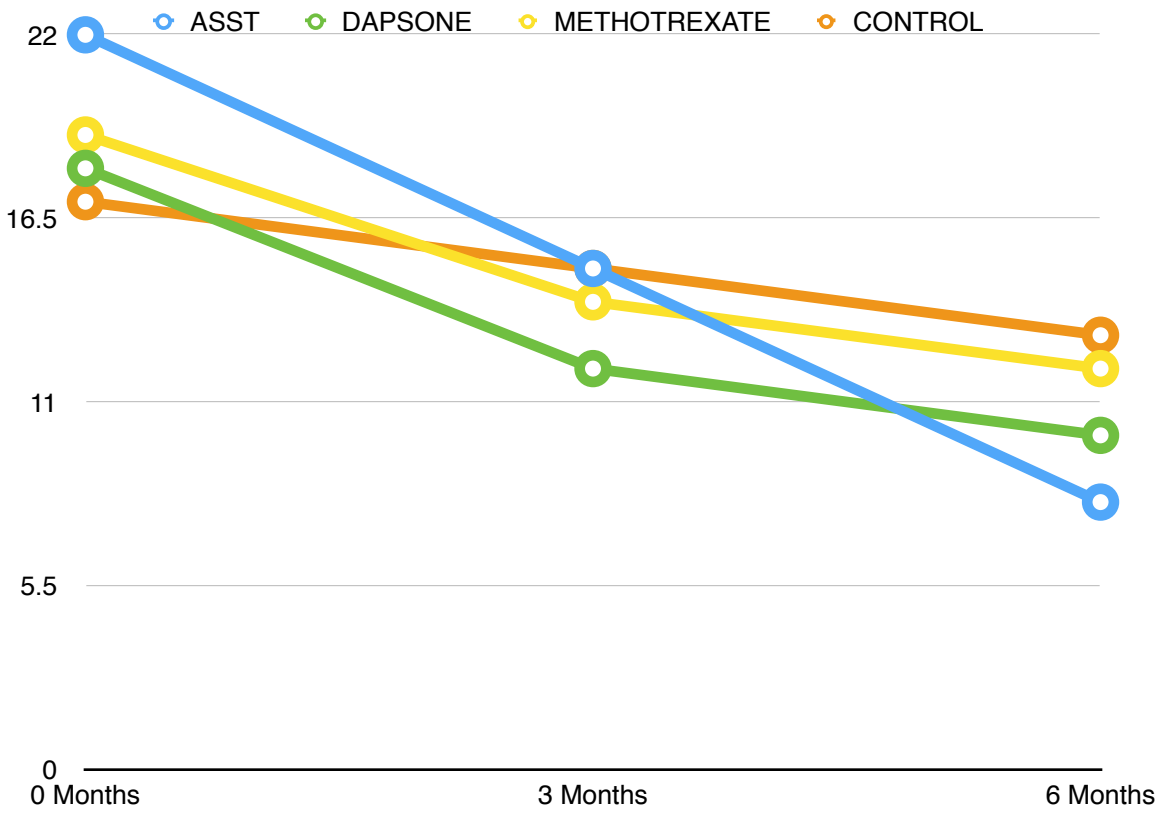
Mean DLQI score for all patients based on treatment offered



Mean DLQI score for patients showing good response based on treatment offered



Mean DLQI score for patients showing average response based on treatment offered



Mean DLQI score for patients showing poor response based on treatment offered

The mean DLQI score across all the treatment groups when compared showed that, patients treated with ASST had the fastest and the maximal response. Both the initial response and the end point was better in ASST patients. Control group patients showed no significant improvement in DLQI score. The dapsone and methotrexate treated patients had similar response profile but there was a difference in the number of patients responding.

TABLE XIV : Shows P values of Response to treatment comparing two groups

Groups compared	P - Values
ASST vs Control	0.001
Dapsone Vs Control	0.014
Methotrexate vs Control	0.022
ASST vs Dapsone	0.035
ASST vs Methotrexate	0.030
Dapsone vs Methotrexate	0.184

This table shows P values by comparing the four groups with one another. There is a statistically significant difference in response to treatment to all three groups when compared to control, with it being highly significant in the ASST group. On comparing ASST with dapsone or methotrexate, there is again a statistically significant difference in response while there was no statistically significant difference when comparing dapsone and methotrexate.

TABLE XV : Prevalence of side effects in each treatment group

	No. of Patients	Total patients treated	Percentage
ASST	0	30	0
Methotrexate	4	30	13.33
Dapsone	2	30	6.67
Control	0	30	0
Total	**6**	**120**	**5**

Side effects were more common in patients taking methotrexate with four out of thirty patients experiencing minor side effects while two patients taking dapsone also had documented side effects.

Discussion

DISCUSSION

This prospective, observational and comparative study was conducted among 120 purposively selected patients with chronic urticaria presenting to the Department of Dermatology, Madras Medical College and Rajiv Gandhi Government General Hospital. The study was carried out with a view to determine the factors responsible for chronic urticaria and to compare the efficacy of ASST, Dapsone and Methotrexate as treatment modalities for patients with chronic urticaria. They were compared against a control group of patients treated with anti-histaminic alone.

Age of 120 patients ranged from 18-56 years. Most of the patients (100, 83.33 %) were in between 18-39 years; with mean age 30.51 years and standard deviation 3.81 years. Eighty five patients were females (70.83%) and thirty five patients were males (29.17%).

Out of 120 patients, forty eight patients (40%) presented within three to six months of onset of symptoms, while forty one patients (34.17%) presented between six to nine months of onset. Twelve patients (10%) presented between six weeks to three months while seventeen patients (14.17%) presented between nine to twelve months. Two patients (1.67%) presented more than a year after onset of treatment. All these patients had not received any treatment apart from

antihistaminics during that period.

An analysis of the common precipitating factors in these patients showed that allergy to food is the more prevalent factor seen in eighteen patients (15%). ENT and Dental infections was seen in twelve patients (10%). Allergy to inhalants like house dust, pollen etc was seen in twelve patients (10%). Drugs was the precipitating factor in eight patients (6.67%). Sixty six patients (55%) had no specific precipitating or aggravating factor.

Atopy is syndrome characterised by a tendency to be “hyperallergic”. Naturally these people have a predisposition to develop chronic urticaria. In our study, twenty six patients (21.67%) had features of atopy.

Hypothyroidism is a commonly encountered coexisting disease seen in patients with chronic urticaria. A possible auto immune mechanism being a causative factor for both these diseases has been hypothesised. In our study twenty one patients (17.5%) had hypothyroidism. Bronchial asthma, an indicator of atopy, was seen in twelve patients (10%). Other systemic comorbidities like Diabetes Mellitus was seen in nine patients (7.5%), Systemic Hypertension in four patients (3.3%) and both in another four patients (3.3%)

Autologous Serum Skin Test was done to all the patients in the study. Around forty four of the 120 patients were positive for ASST (36.67%). There was difference in gender among the ASST positive patients. Only seven patients (5.83%) were males while the remaining thirty seven patients (30.83%) were females. Seventy six patients (63.33%) were negative for ASST.

The 120 patients in the study were divided into four groups of 30 patients each and started on respective treatment regimen. In ASST group, there were 7 male patients and 23 female patients. In methotrexate group, there were 10 male patients and 20 female patients. In dapsone group, there were 9 male patients and 21 female patients. In control group, there were 9 male patients and 21 female patients. The patients were divided in such a way that similar number of patients from each age set were included in each group. An average of fifteen patients in 18 - 29 age group, nine patients in 30 - 39 age group, four patients in 40 - 49 age group and two patients in 50 - 59 age group were present in each treatment group.

The response to treatment was analysed in all the treatment groups based on reduction in the DLQI score and UAS score and symptomatic improvement. The response was then graded as good, average and poor.

Among the thirty patients treated with ASST, twenty two patients (73.33%) had good response to treatment, with six patients (20%) showing average response and only two patients (6.67%) showed poor response to treatment.

Of the thirty patients managed with dapsone, fifteen patients (50%) showed good response to treatment. Thirteen patients (43.33%) showed average response to treatment with dapsone while two patients (6.67%) showed poor response.

In patients treated with methotrexate group, ten patients (33.33%) showed good response to treatment, fourteen patients (46.67%) showed average response to treatment while six patients (20%) had poor response to treatment.

Comparing this with the control group, around sixteen patients (53.33%) showed poor response to treatment, with ten patients (33.33%) having average response and only four patients (13.33%) had improvement in their symptoms.

ASST compared favourably to the other two drugs with nearly three fourths of the patients having significant symptomatic improvement while only fifty and thirty three percent of patients of the dapsone and methotrexate group had a good response to treatment.

Both the methotrexate and dapsone group patients showed a better response to treatment than the control group with only two patients in the dapsone group and six patients in the methotrexate group showing poor response compared to the sixteen patients in the control group. Both the methotrexate and dapsone group patients had similar number showing average response to treatment.

With regards to relation of age and sex to response to treatment, females had a slightly improved tendency to respond to treatment, but this was not significant. The increased numbers can be attributed to the generally more prevalence among the female sex. Similarly, age seemed to have no effect on the response to treatment, with patients across all age groups showing same pattern of response in all the four treatment groups.

ASST positivity has a significant relation with better response to treatment. ASST positive patients generally had a good response to treatment with poor response seen in only five patients (11%) across all groups, with four of those patients being in the control group. Nearly eighty percent of the patients in the ASST treatment group had good response to treatment, while fifty percent of the patients in the methotrexate and dapsone group showed good response. The above findings showed that treatment with autologous skin serum for patients who are ASST positive is the best option.

An analysis of the DLQI scores, showed that patients having a mean DLQI score in the lower range generally had a good response to treatment. The ASST group patients showed the maximal reduction in DLQI score between baseline and the follow up value at six months with a drop of more than ten points seen even in patients with poor response. ASST group patients also had a high reduction in

DLQI score soon after initiating treatment, with near complete recovery seen as soon as completing treatment.

In the dapsone group, the initial response is lower than that of ASST and the net reduction is also lower than that of ASST. The end points are comparable in each response group separately but is not reliable as fewer patients showed good response.

In methotrexate group, the initial response was lower than both dapsone and ASST, with symptomatic improvement becoming evident only towards the end of treatment or even after treatment. The net reduction in DLQI score at the end of six months was similar to dapsone group.

None of these patients surprisingly showed any signs of relapse. All the three treatment groups patient showed at the least a partial response with definite reduction in symptomatology after starting treatment.

Four patients (13.33%) treated with methotrexate had side effects while two patients (6.67%) who took dapsone had side effects. None of the ASST group patients had any side effects.

LIMITATIONS OF STUDY

As this study has been carried out over a limited period of time with a limited number of patients it was not large enough to be of reasonable precision. All the available modalities of treatment were not assessed. All the facts and figures mentioned here may considerably vary from those of large series covering wide range of time, but still then, as the cases of this study were collected from a tertiary level hospital in our country, this study has some credentials in reflecting the facts regarding factors responsible for chronic urticaria and the available treatment options and the most favourable modality of treatment for patients.

SUMMARY

Chronic uritcaria, is a disease affecting 0.5 - 1 % of the population at any given time. It is a distressing disease encountered frequently in clinical practice. the current mainstay of therapy is the use of second-generation, non sedating anti-histamines. However, in patients who do not respond satisfactorily to these agents, a variety of other drugs are used.

In our study we have compared the efficacy of ASST, Dapsone and Methotrexate in the treatment of chronic urticaria. The following conclusions were reached.

Age and Sex Distribution :

Young females were the most commonly involved group. Twenty to thirty years was the susceptible age group along with female gender. This is in accordance with other Indian studies regarding the epidemiology of the disease.

Precipitating Factors :

One or other form of precipitating factor was present in more than half of all the patients involved in the study. The most commonly implicated precipitating factor in our study was food allergens followed by infections and inhalants. A study by Godse et al showed that infections and food allergens were important precipitating factors in the Indian population.

Atopy :

A basic tendency for allergic reactions, as indicated by the presence of atopic features was seen in twenty percent of all patients

Co - Morbid Factors :

Our study showed a significant level of prevalence of hypothyroidism among all treatment groups with bronchial asthma also widely prevalent. Both of these are considered to be related with pathophysiological process of chronic urticaria. Few people were diabetic or hypertensive, all of them belonging to the older age group and this had no significant correlation

Prevalence of ASST positivity :

Out of 120 patients in the study, 44 patients turned out to be positive for Autologous Serum Skin Test. Of these 37 patients were females and only 7 patients were males. This suggests that auto immunity may be the significant mechanism of chronic urticaria in our population.

Comparison of the treatment groups :

In the ASST group, all patients had a significant reduction in their DLQI score with only two patients having poor response, which was explained by the fact that both those patients had a severe initial presentation. The response was especially good among those in whom the autologous serum skin test was positive. This response to ASST was found to be in concurrence with studies by Bajaj et al

and Staubach et al. Compliance was good and there was no evidence of relapse. The only factor which hinders with their use, especially in a government setup, is the technological expertise and the availability of centrifuge machines

In the Dapsone group, again there was a statistically significant improvement in response compared to the control group, but they compared unfavourably with ASST treatment group. The initial response was slower than that of ASST but the end point was similar especially in those responding well to treatment. There was good compliance, even though a couple of patients had minor side effects. These findings had concordance with studies conducted by Cooke et al, Engen et al and Boehm et al.

In the methotrexate group, there was a comparatively slower reduction in the DLQI score with response starting only near the end of treatment. They were better off than the control group but both the initial response and the end points were poor when compared to ASST. They had a comparable response to the patients treated with dapsone but its use is limited in patients with anaemia and deranged LFT. With the anaemia commonly prevalent in our population this limits its use in patients. Moreover, the incidence of side effects was more in this group. Studies by Sharma et al advised the use of methotrexate in those with chronic recalcitrant urticaria who don't respond to other treatment modalities.

CONCLUSIONS

On the basis of the findings of the study, the following recommendations can be made:

1. Proper evaluation is mandatory to find out the presence of precipitating factor and if present, management of the same
2. ASST can be considered as a first line of treatment, in patients with chronic urticaria, especially in those who are positive for Autologous Serum Skin Test. The preferred regimen being 2ml of autologous serum given as deep intramuscular injections once a week for nine weeks
3. Dapsone can be considered for patients refractory to treatment. The regimen being 50mg daily for a period of 12 weeks.
4. Methotrexate is recommended as last resort, in patients who are refractory to other modalities of treatment. Side effects profile and its contraindication in patients with haematological problems, restrict its more common usage
5. A randomized, controlled study with prolonged follow up and involving much more modalities of treatment is necessary to devise an accepted management protocol for patients with chronic urticaria.

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APPENDIX - I : ETHICAL COMMITTEE CLEARANCE

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 011 25363970

CERTIFICATE OF APPROVAL

To
Dr. Meenakshi M,
Postgraduate M.D.D.V.L.(Dermatology, Venereology and Leprosy),
Madras Medical College,
Chennai – 600 003.

Dear Dr.Meenakshi M,

The Institutional Ethics Committee has considered your request and approved your study titled **"A comparative study on the efficacy of Methotrexate Vs Dapsone Vs ASST (Autologous Serum Skin Therapy) for treatment of chronic urticaria". No.15112014.**

The following members of Ethics Committee were present in the meeting held on 11.11.2014 conducted at Madras Medical College, Chennai-3.

1. Dr.C.Rajendran, M.D.,	: Chairperson
2. Dr.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.R.Nandini, M.D., Inst.of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor, Inst.of Surgery, MMC	: Member
6. Prof.Md.Ali, M.D., D.M., Prof. & HOD of Medl.G.E., MMC	: Member
7. Prof.K.Ramadevi, Director i/c, Inst.of Biochemistry, MMC	: Member
8. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
9. Prof.S.G.Sivachidambaram, M.D., Director i/c, Inst.of Internal Medicine, MMC	: Member
10. Thiru S.Rameshkumar, Administrative Officer	: Lay Person
11. Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
12. Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

21/11/14

Member Secretary, Ethics Committee
VICE PRINCIPAL
MADRAS MEDICAL COLLEGE
CHENNAI-3.

Appendix-II

DATA COLLECTION SHEET

Name: Age: Sex:

IP No. :

ON ADMISSION:

Main Complaints :

Time of onset :
Duration of urticaria :
Duration of individual lesion :
H/o Atopy :
Family h/o autoimmune diseases :
Co – Morbid Illness :
Significant Past History :

CLINICAL EXAMINATION:

Pulse : BP :

RR : Temp :

Pallor : Icterus :

CVS : RS :

P/A :

Dermatological Examination :

- Morphology of lesion :
- Distribution :
- Features of systemic involvement :
- Evidence of infection :

INVESTIGATIONS :

CBC : ESR :

Liver Function Test : Renal Function Test :

CXR :

Autologous Serum Skin Test :

TREATMENT :

Group :

Regimen given :

FOLLOW UP :

Onset of remission :

Duration of remission :

Side effects :

DERMATOLOGY LIFE QUALITY INDEX

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ⇛ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	 Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	 Not relevant ❒

DLQI Score : The scoring of each question is as follows:

Very much scored 3

A lot scored 2

A little scored 1

Not at all/ Not relevant/ Question unanswered scored 0

Question 7: "prevented work or studying" scored 3

UAS (Urticaria Activity Score) :

Score	Wheal	Pruritis
0	None	None
1	Mild (<20 wheals/24h)	Mild
2	Moderate (20-50 wheals/24h)	Troublesome but doesn't interfere with sleep
3	Severe (>50 wheals/24h or large confluent areas of wheals)	Severe, interferes with normal activity and sleep

	UAS SCORE	**DLQI SCORE**
Start of Treatment		
End of Treatment		
6 months following treatment		

INFORMATION SHEET

TITLE : **"A Comparative Study On The Efficacy Of Methotrexate Vs Dapsone Vs ASST (Autologous Serum Skin Therapy) For Treatment Of Chronic Urticaria"**

Name of Investigator : Dr. Meenakshi M. Name of Participant :

Purpose of Research : The purpose of the study is to compare the efficacy of the various modalities of treatment like methotrexate, dapsone and ASST (Autologous Serum Skin Therapy) for treatment of chronic urticarial.

Study Design : Prospective Observational Study

Study Procedures : Patient will be subjected to routine investigations, Autologous Serum Skin Test & Chest X ray. The patients are then randomly grouped into 4 groups and undergo treatment.

Possible Risks : No risks to the patient

Possible benefits

To patient : Patient is provided an alternative modality of treatment which will help in remission of their disease.

To doctor & to other people : If this study gives positive results, it can help determine the most effective treatment and the treatment protocol for patients with chronic urticaria. This will help in providing better and complete treatment to other patients in future.

Confidentiality of the information obtained from you : The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared

Can you decide to stop participating in the study : Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time

How will your decision to not participate in the study affect you : Your decision will not result in any loss of benefits to which you are otherwise entitled.

Signature of Investigator Signature of Participant

Date :

Place :

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சி எண் : உள் நோயாளி எண் :

பங்கேற்பாளரின் பெயர் : வயது : ஆண் / பெண் :

சென்னை ராஜீவ் காந்தி அரசு பொது மருத்துவமனையில் சுணைத்தடிப்பு நோயிற்கு டாப்சோன் (Dapsone), மீதோதிரெக்ஸ்செட் (Methotrexate) மற்றும் எ.எஸ்.எஸ்.டி (ASST) போன்ற வை வதியங்களின் பயனுடைமை பற்றி அறிவதற்கான ஆராய்ச்சி நடைபெற உள்ளது. இந்த ஆராய்ச்சியில் தாங்கள் பங்கு பெ பற நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் தங்களுக்கு இரத்த பரிசோதனை செ செய்யப்பட்டு பின்பு தங்களுக்கு கிடைக்க வே வண்டிய வைத்தியம், ஆராய்ச்சியின் தேவையின் பேரில் அளிக்க படும்..

இந்த ஆராய்ச்சியின் மூலம் தங்களின் சிகிச்சை எவ்விதத்திலும் பாதிப்படையாது. இந்த ஆராய்ச்சியின் முடிவுகள் நேர்மறை முடிவுகளாக இருப்பின் அது பின் வரும் நோயாளிகளுக்கு பயனுள்ளதாகவும் இருக்கும்.

இந்த ஆராய்ச்சியினால் தங்களின் நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்பு அடையாது என்று தெ தரிவித்து கொள்கிறோம். முடிவுகளை அல்லது கருத்துகளை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது பெ பயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்து கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களது விருப்பத்தின் பேரில் மட்டும் தான். மேலும் இந்த ஆராய்ச்சியின் முடிவுகள் தங்களுக்கு அறிவிக்கப்படும் என்றும் தெ தரிவித்து கொள்கிறோம். மே மலும் நீங்கள் எந்நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்து கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

நாள் :
இடம் :

PATIENT CONSENT FORM

Study Detail	:	**"A COMPARATIVE STUDY ON THE EFFICACY OF METHOTREXATE VS DAPSONE VS ASST (AUTOLOGOUS SERUM SKIN THERAPY) FOR TREATMENT OF CHRONIC URTICARIA"**
Study Centre	:	Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age	:	
In Patient Number	:	

Patient may check (☑) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ❑

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ❑

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ❑

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ❑

I hereby consent to participate in this study ❑

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests and to undergo treatment ❑

Signature/thumb impression

Patient's Name and Address:

Signature of Investigator

Study Investigator's Name:

Dr. MEENAKSHI M.,

ஆராய்ச்சி ஒப்புதல் படிவம்

ஆராய்ச்சியின் தலைப்பு : சுணைத்தடிப்பு நோயிற்கு டாப்சோன் (Dapsone), மீதோதிரெக்ஸ்செட் (Methotrexate) மற்றும் எ.எஸ்.எஸ்.டி (ASST) போன்ற வைதியங்களின் பயனுடைமை பற்றி அறிவதற்கான ஆராய்ச்சி

பங்குகொள்வரின் பெயர் :

ஆராய்ச்சி செய்பவரின் பெயர் : மீனாட்சி மீ.

இடம் : ராஜீவ் காந்தி அரசு பொது மருத்துவமனை, சென்னை – 600003

_____ எனும் நான், எனக்கு கொடுத்துள்ள தகவல் தாளை படித்து புரிந்து கொண்டேன். நான் பதினெட்டு வயதை கடந்துள்ளதால், என்னுடைய சுயநினைவுடனும், முழு சுகந்திரதுடனும், இந்த ஆராய்ச்சியில் என்னை சேர்த்துக்கொள்ள சம்மதிக்கிறேன்.

நான், எனக்கு கொடுத்துள்ள தகவல் தாளை படித்து புரிந்து கொண்டேன்.

எனக்கு இந்த ஆராய்ச்சியின் ஒப்புதல் படிவம் விளக்க பட்டுள்ளது.

எனக்கு இந்த ஆராய்ச்சியின் நோக்கமும், விவரங்களும் விளக்கப்பட்டது.

எனக்கு என்னுடைய உரிமைகள் பற்றி விளக்கப்பட்டது.

இந்த ஆராய்ச்சியில் இருந்து நான் என் நேரமும் பின் வாங்கலாம் என்றும், அதனால் எந்த பின் விளைவும் ஏற்படாது என்று புரிந்து கொண்டேன்.

என்னை பற்றி எந்த தகவலும், அடையாளங்களும் வெளியிடப்பட மாட்டது என்பதையும் புரிந்து கொண்டேன்.

என்னுடைய முழு சுகந்திரதுடனும் இந்த ஆராய்ச்சியில் சேர்த்து கொள்ள சம்மதிக்கிறேன்.

பங்கேற்பாளர் கையொப்பம் ஆராய்ச்சியாளர் கையொப்பம்

நாள் :

இடம் :

Appendix – III

Statistical formula

A. Sample size:

To determine the sample size, this formula was used; $n = \frac{z^2 pq}{d^2}$

Where,

n = the desired sample size,

z = the standard normal deviate, usually set at 1.96 at 5% level,

which corresponds to 95% confidence level,

p = proportion of population, q

= 1- p

d = the degree of accuracy level considered as 5.0 %,

which assumes 0.05

If population size, N < 10,000 than the required sample size is very much smaller which was calculated by the following formula –

$$n_f = \frac{n}{1 + \frac{n}{N}}$$

Where,

n_f = the desired sample size, when population size, N < 10,000

n = the desired sample size, when population size, N > 10,000 N

= the roughly estimated population size.

B. Arrithmatic mean, $X = \frac{\sum fx}{N}$ (for grouped data)

C. Standard deviation , $SD = \sqrt{\sum (X- \bar{X})^2}$

('O' indicates observed value and 'E' indicates expected value)

D. $$Z = \frac{P_1 - P_2}{\sqrt{\left[\frac{P_1 Q_1}{N_1} + \frac{P_2 Q_2}{N_2}\right]}}$$

P_1 indicates proportion in first group

P_2 indicates proportion in second group

$Q_1 = 100 - P_1$

$Q_2 = 100 - P_2$

N_1 indicates sample size of first group

N_2 indicates sample size of second group.

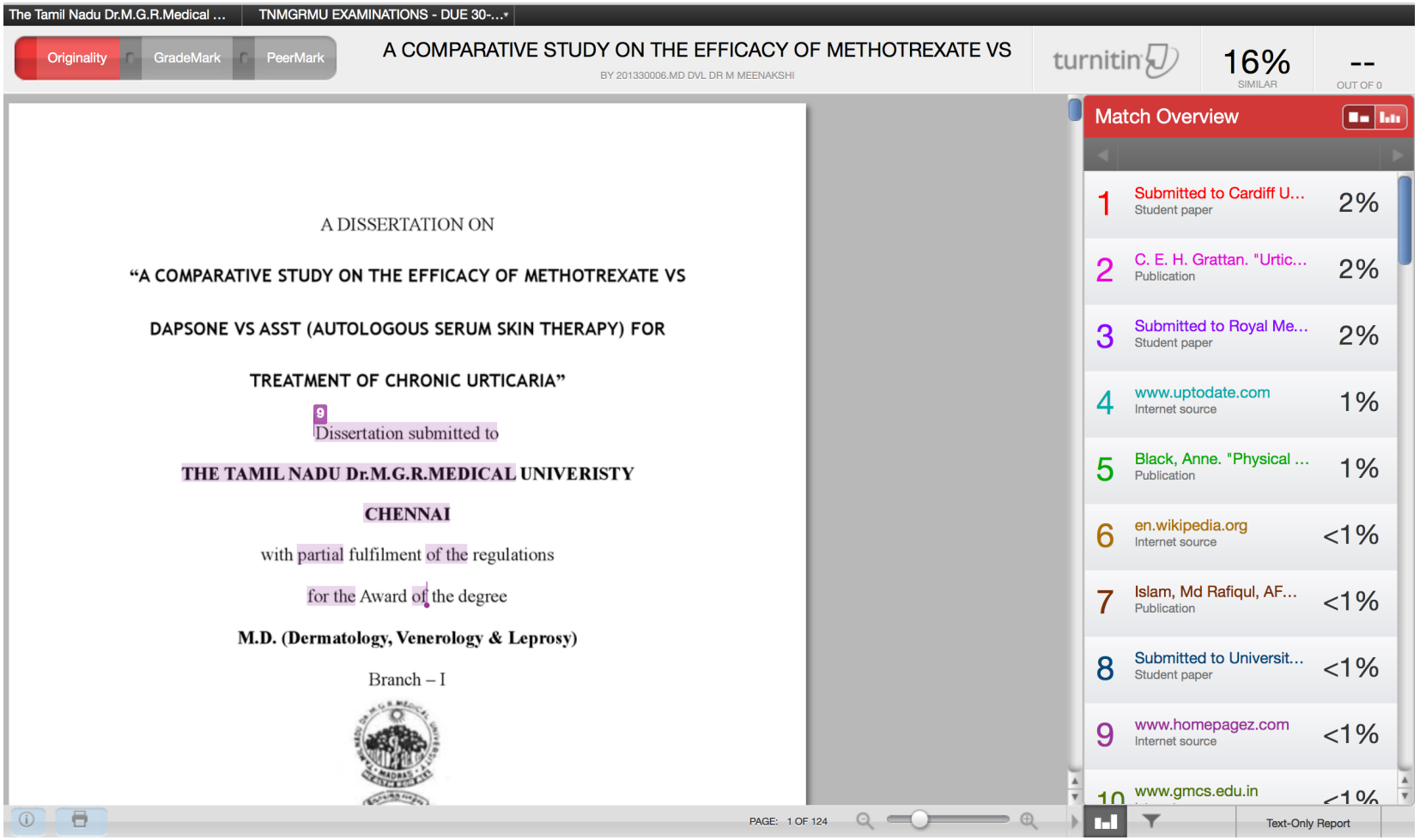
E. $$SD = \sqrt{\frac{\sum (X - \bar{X})}{(N-1)}}$$

Here, $\bar{X}$ indicates mean value

X indicates individual value

N indicates sample

Appendix-IV: Plagiarism



APPENDIX V : MASTERCHART

S No.	Name	Age	Sex	Ip No	Complaints		Atopy	Co Morbidity	Derm Examination	ENT/ Dental Examination	CBC	RFT	LFT	ASST	Treatment	Side Effects	UAS			DLQI			Conclusion
					Duration	Prec. Factor			Morphology														
1	Sathish	23	M	186128	5	Inhalant	-	BA	Papule	N	N	N	N	-	Asst	-	5	3	2	20	8	4	Average
2	Anandan	28	F	185868	6	Infection	+	BA	Plaque	Infection	Es	N	N	-	Control	-	4	2	2	12	10	6	Average
3	Suganya	19	F	76588	9.5	-	-	-	Wheal	N	N	N	N	-	Asst	-	3	0	0	10	3	1	Good
4	Chellamal	24	F	10261	5	-	-	-	DG	N	N	N	N	+	Control	-	2	0	0	6	4	3	Good
5	Kumari	30	F	70332	6.5	-	-	-	Plaque	N	N	N	N	-	Metho	-	4	3	0	9	4	1	Good
6	Keerthana	19	F	70924	10.5	Infection	-	Hypothy	Papule	Infection	N	N	N	+	Asst	-	6	2	0	16	6	2	Good
7	Dalin Mary	28	F	70489	4.5	Food	-	BA	Wheal	N	Es	N	N	-	Dapsone	+	4	2	1	13	9	7	Average
8	Kanya	29	F	70438	5.5	Food	+	-	Plaque	N	Es	N	N	-	Dapsone	-	4	1	0	9	4	0	Good
9	Jagadesh	27	M	88085	4.5	-	-		Papule	N	N	N	N	-	Dapsone	-	3	0	0	7	2	1	Good
10	Lakshmi	34	F	76944	4	Inhalant	-	-	Wheal	N	Es	N	N	-	Asst	-	3	1	0	10	5	0	Good
11	Mary	25	F	70357	7.5	-	-	Hypothy	Plaque	N	N	N	N	-	Metho	-	4	3	1	19	11	3	Average
12	Vijayan	29	M	37359	6	-	-	-	DG	N	N	N	N	-	Dapsone	-	2	0	0	8	4	2	Good
13	Indumathy	25	F	68037	3	-	+	-	Wheal	N	N	N	N	-	Control	-	4	3	4	15	10	12	Poor
14	Kupama	37	F	68166	2.5	Inhalant	-	HTN	Plaque	N	N	N	N	+	Control	-	3	2	2	18	17	14	Poor
15	Farzana	34	F	76793	6	Food	+	DM	Wheal	N	Es	N	N	-	Metho	-	3	1	1	12	9	6	Average
16	Sanas Begam	35	F	1706	5	-	-	-	Wheal	N	N	N	N	-	Dapsone	-	2	0	0	6	2	0	Good
17	Suresh	37	M	165334	4.5	Infection	-	-	Plaque	Infection	N	N	N	-	Metho	-	4	3	2	10	7	5	Average
18	Nanda	40	M	165314	9	-	+	Hypothy	DG	N	Es	N	N	-	Control	-	5	3	2	9	7	4	Average
19	Nisha	22	F	61741	8	-	-	-	Papule	N	N	N	N	+	Asst	-	2	0	0	8	3	0	Good
20	Baby	40	F	77136	4.5	-	-	DM	Plaque	N	N	N	N	-	Metho	+	5	4	2	22	18	14	Poor
21	Chitra	25	F	77145	2.5	Food	-	-	Wheal	N	Es	N	N	+	Dapsone	-	2	1	1	12	9	3	Average
22	Manikandan	21	M	81110	11.5	Drug	-	-	Wheal	N	Es	N	N	+	Metho	-	5	2	2	20	16	14	Poor
23	Alamelu	42	F	57243	3.5	-	+	Hypothy	Plaque	N	N	N	N	-	Metho	-	5	3	2	9	6	5	Average
24	Purushothaman	29	M	81865	5	Inhalant	-	-	Wheal	N	Es	N	N	+	Control	-	3	2	1	10	8	6	Average
25	Mohana	45	F	76819	7.5	-	-	-	Wheal	N	An	N	N	+	Asst	-	4	2	0	10	4	1	Good
26	Gajalaxmi	45	F	76929	10.5	Infection	+	DM	Plaque	Infection	Es	N	N	-	Control	-	4	3	2	16	12	11	Poor
27	Jayalaxmi	38	F	6133	9	-	-	-	Wheal	N	N	N	N	-	Control	-	2	1	1	8	4	2	Good
28	Lavanya	21	F	68446	5	Food	-	-	Wheal	N	N	N	N	+	Dapsone	-	3	1	0	9	5	6	Average
29	Gandimathy	35	F	77189	9	-	-	-	Plaque	N	N	N	N	-	Dapsone	+	4	2	2	18	12	10	Poor
30	Ravi	55	M	165174	7.5	Drug	+	HTN	DG	N	N	N	N	-	Metho	-	3	1	0	9	5	2	Good

S No.	Name	Age	Sex	Ip No	Complaints			Co Morbidity	Derm Examination	ENT/ Dental Examination	CBC	RFT	LFT	ASST	Treatment	Side Effects	UAS			DLQI			Conclusion
31	Valli	38	F	68068	7	-	-	HTN	Wheal	N	N	N	N	+	Metho	-	2	0	0	10	5	2	Good
32	Sakthiselvi	24	F	77270	3	-	+	Hypothy	Plaque	N	Es	N	N	+	Control	-	4	3	1	14	10	8	Average
33	Kuttiyamal	38	F	77288	4	Drug	-	-	Wheal	N	An	N	N	+	Asst	-	4	2	2	16	8	6	Average
34	Chinna	28	M	165252	3.5	-	-	-	Wheal	N	N	N	N	-	Dapsone	-	6	4	3	18	12	8	Average
35	Karthik	18	M	45446	4.5	-	-	Hypothy	Wheal	N	N	N	N	-	Asst	-	4	0	0	12	4	1	Good
36	Ameena	25	F	68572	2.5	Infection	+	-	Wheal	Infection	Es	N	N	-	Dapsone	-	4	2	1	9	5	3	Good
37	Malliga	18	F	62727	2	-	-	-	Plaque	N	N	N	N	+	Metho	-	2	1	0	9	4	1	Good
38	Raj	29	M	81031	8	-	-	-	Wheal	N	N	N	N	-	Control	-	5	3	2	22	18	15	Poor
39	Jothy	45	F	753474	5	-	+		Wheal	N	N	N	N	+	Dapsone	-	3	1	1	19	8	5	Average
40	Deepak	21	M	81101	3	-	-	-	Plaque	N	N	N	N	-	Dapsone	-	3	1	1	8	3	1	Good
41	Arthi	22	F	68645	2.5	AQUA	-	Hypothy	DG	N	N	N	N	+	Control	-	2	0	0	6	4	2	Good
42	Meenatchi	25	F	73441	2	-	-	-	Papule	N	N	N	N	-	Asst	-	3	1	0	8	2	0	Good
43	Nithya	23	F	14787	5	Food	+	-	Wheal	N	Es	N	N	-	Control	-	6	4	3	24	20	18	Poor
44	Amutha	39	F	79937	5	-	+	DM	Wheal	N	N	N	N	-	Asst	-	2	1	0	9	2	1	Good
45	Senthilkumar	29	M	165278	5.5	AQUA	-	-	Plaque	N	N	N	N	-	Metho	-	5	3	2	9	7	4	Average
46	Vasantha	22	F	74870	9	Drug	-	Hypothy	Wheal	N	N	N	N	-	Asst	-	3	0	0	5	0	0	Good
47	Mahalaxmi	34	F	74002	8	Food	-	-	Papule	N	N	N	N	-	Dapsone	-	2	1	0	8	3	1	Good
48	Devi	29	F	74926	8	Food	+	BA	Wheal	N	Es	N	N	+	Metho	-	4	2	1	18	7	3	Average
49	Tamilarasi	30	F	74133	9.5	-	-	-	Wheal	N	N	N	N	+	Asst	-	3	0	0	16	2	0	Good
50	Velu	43	M	162918	5	Infection	-	-	Plaque	Infection	N	N	N	-	Metho	+	5	2	3	19	9	12	Poor
51	Pavithra	18	F	66644	10.5	-	-	Hypothy	Wheal	N	N	N	N	+	Control	-	2	1	1	10	9	5	Average
52	Suri	31	F	750077	5	Food	-	-	DG	N	N	N	N	+	Dapsone	-	3	1	1	18	4	2	Good
53	Kalaivani	27	F	75087	8	-	-	-	Wheal	N	N	N	N	-	Metho	-	5	2	2	15	10	7	Average
54	Imran	18	M	809892	4	Food	-	-	Plaque	N	N	N	N	+	Asst	-	3	0	0	12	5	2	Good
55	Mohan	35	M	80899	3	Food	+	BA	Wheal	N	Es	N	N	+	Control	-	3	1	1	12	8	5	Average
56	Thilaga	45	F	666666	12	Food	-	Hypothy	Wheal	N	N	N	N	-	Metho	-	4	1	2	12	7	4	Average
57	Sathiya	22	F	74996	2.5	Food	+	BA	Papule	N	Es	N	N	+	Asst	-	4	2	1	14	6	2	Good
58	Glory	22	F	19885	8	AQUA	-	-	Wheal	N	N	N	N	-	Control	-	4	2	3	16	11	12	Poor
59	Mruugesan	50	M	163355	4.5	-	-	-	Plaque	N	N	N	N	-	Asst	-	5	2	2	23	14	10	Poor
60	Mani	50	M	163369	4.5	-	-	BA	Wheal	N	N	N	N	+	Metho	-	2	1	0	8	4	1	Good

S No.	Name	Age	Sex	Ip No	Complaints			Co Morbidity	Derm Examination	ENT/ Dental Examination	CBC	RFT	LFT	ASST	Treatment	Side Effects	UAS			DLQI			Conclusion
61	Kamatchi	35	F	673411	5	Infection	-	-	Wheal	Infection	N	N	N	+	Metho	+	3	1	1	7	2	1	Good
62	Vinoth	23	M	22282	4	-	-	-	Wheal	N	N	N	N	-	Metho	-	3	2	1	9	6	5	Average
63	Anusya	24	F	67383	6	-	-	Hypothy	Wheal	N	N	N	N	-	Asst	-	5	3	2	12	6	5	Average
64	Revathy	23	F	71872	2.5	Food	+	-	Plaque	N	N	N	N	+	Asst	-	4	2	2	20	10	6	Average
65	Shameena	38	F	72404	9	Food	-	DM	Wheal	N	Es	N	N	-	Dapsone	-	3	1	0	10	8	5	Average
66	Srinivasan	23	M	160354	9	-	-	-	DG	N	N	N	N	-	Dapsone	-	4	2	1	13	8	5	Average
67	Ravi	50	M	160427	10	-	-	DM/HTN	Wheal	N	N	N	N	-	Control	-	5	3	3	21	17	13	Poor
68	Kavitha	23	F	67641	6	Infection	+	-	Wheal	Infection	Es	N	N	-	Dapsone	-	4	2	2	10	7	4	Average
69	Kasthuri	45	F	1781	13	-	-	Hypothy	Plaque	N	An	N	N	-	Control	-	3	1	1	9	6	5	Average
70	Annalaxmi	42	F	73322	8	Inhalant	-	DM	Papule	N	N	N	N	-	Asst	-	3	1	1	9	4	1	Good
71	Kalaiselvi	37	F	73370	8	Infection	+	BA	Wheal	Infection	N	N	N	+	Control	-	5	3	2	18	14	10	Poor
72	Gopi	31	M	160455	5	-	-	-	Wheal	N	N	N	N	-	Dapsone	-	4	3	2	14	8	4	Average
73	Santhy	25	F	65208	10	-	-	-	Wheal	N	N	N	N	+	Asst	-	2	0	0	10	5	1	Good
74	Divya	21	F	73545	3	-	-	-	Wheal	N	N	N	N	-	Asst	-	2	1	1	8	5	2	Good
75	Sudha	21	F	1358	12	-	-	Hypothy	Plaque	N	N	N	N	-	Dapsone	-	5	2	2	18	12	10	Poor
76	Anusha	19	F	73241	3	Drug	-	BA	Wheal	N	N	N	N	-	Control	-	4	3	2	15	11	10	Poor
77	Pradeep	22	M	82681	3	Inhalant	+	Hypothy	Wheal	N	Es	N	N	-	Metho	-	5	4	3	18	12	7	Average
78	Gowri	23	F	6618	4.5	-	-	-	Wheal	N	N	N	N	-	Metho	-	5	4	3	18	16	13	Poor
79	Yuvanjali	20	F	75643	3	Inhalant	-	-	Plaque	N	N	N	N	-	Control	-	2	1	0	5	3	3	Good
80	Surendrakumar	23	M	6044	7	-	-	-	Papule	N	N	N	N	-	Asst	-	4	2	2	16	10	5	Average
81	Elavarasi	26	F	64253	4.5	-	-	-	Wheal	N	N	N	N	-	Dapsone	-	3	1	1	10	5	2	Good
82	Malliga	35	F	71572	9	-	-	DM	DG	N	N	N	N	+	Metho	-	3	1	0	10	4	1	Good
83	Sumathy	35	F	71471	9	-	+	-	Wheal	N	Es	N	N	+	Metho	-	3	3	1	16	10	8	Average
84	Devaki	37	F	71416	8	-	-	Hypothy	Plaque	N	N	N	N	-	Dapsone	-	2	0	0	8	3	0	Good
85	Amlu	30	F	64541	8	Food	+	BA	Wheal	N	N	N	N	+	Asst	-	3	0	0	10	2	0	Good
86	Elumalai	26	M	160477	4	Inhalant	-	-	Wheal	N	N	N	N	-	Dapsone	-	2	0	0	10	3	1	Good
87	Harikrishnan	56	M	160475	2.5	-	-	DM/HTN	Papule	N	An	N	N	-	Control	-	4	3	3	14	12	11	Poor
88	Nandini	25	F	71498	7	-	-	-	Wheal	N	N	N	N	+	Control	-	3	3	2	14	11	8	Average
89	Devi	24	F	71603	5.5	Inhalant	+	-	Plaque	N	Es	N	N	-	Dapsone	-	5	2	2	12	8	4	Average
90	Anjaladevi	26	F	71537	7.5	-	-	-	DG	N	N	N	N	-	Metho	-	4	3	2	15	12	10	Poor

S No.	Name	Age	Sex	Ip No	Complaints			Co Morbidity	Derm Examination	ENT/ Dental Examination	CBC	RFT	LFT	ASST	Treatment	Side Effects	UAS			DLQI			Conclusion
91	Saraswathy	47	F	71787	8	-	-	DM/HTN	Wheal	N	An	N	N	-	Asst	-	5	3	2	21	15	6	Poor
92	Shanty	44	F	70597	5.5	-	-	DM/HTN	Wheal	N	N	N	N	-	Control	-	5	3	3	20	16	13	Poor
93	Revathy	20	F	71852	6.5	-	-	-	Papule	N	N	N	N	-	Metho	-	3	1	1	8	3	2	Good
94	Elancheliyan	24	M	4292	3.5	-	-	-	Plaque	N	N	N	N	-	Control	-	4	3	2	15	12	10	Poor
95	Sudha	25	F	64439	6	-	-	Hypothy	Wheal	N	N	N	N	+	Control	-	5	3	2	10	8	5	Average
96	Valli	32	F	71507	5	-	-	-	Wheal	N	N	N	N	+	Asst	-	3	0	0	10	3	1	Good
97	Geetha	38	F	71908	3	Inhalant	-	Hypothy	Wheal	N	An	N	N	+	Asst	-	4	2	1	22	7	4	Average
98	Ashwini	21	F	72051	3.5	Infection	-	-	DG	Infection	N	N	N	+	Dapsone	-	4	2	1	10	7	5	Average
99	Dinesh	23	M	82577	7.5	Food	-	-	Plaque	N	Es	N	N	-	Asst	-	2	1	0	5	1	0	Good
100	Amm	35	F	64612	10	-	-	DM	Wheal	N	N	N	N	+	Metho	+	5	3	1	13	9	6	Average
101	Mageswari	32	F	64915	7.5	-	-	-	Wheal	N	N	N	N	+	Dapsone	-	1	0	0	6	2	0	Good
102	Uma	42	F	71897	3	-	-	-	Papule	N	N	N	N	-	Metho	-	4	2	2	12	8	4	Average
103	Malathy	25	F	64961	4	Infection	-	Hypothy	Wheal	Infection	N	N	N	+	Control	-	5	3	2	17	12	10	Poor
104	Abhilash	22	M	142041	6.5	-	-	-	Plaque	N	N	N	N	-	Metho	-	5	3	2	18	13	10	Poor
105	Inbasekar	53	M	142065	6	AQUA	-	-	DG	N	N	N	N	-	Metho	-	2	1	0	8	2	2	Good
106	Vanitha	21	F	64531	2.5	-	-	-	Wheal	N	Es	N	N	-	Dapsone	-	4	2	2	10	8	4	Average
107	Rani	30	F	71988	6.5	Inhalant	+	BA	Wheal	N	Es	N	N	+	Dapsone	-	2	0	0	10	4	2	Good
108	Suba	27	F	69715	3	-	-	-	Wheal	N	N	N	N	-	Control	-	4	3	3	15	13	10	Poor
109	Velankani	32	F	69805	9	-	-	-	Wheal	N	N	N	N	+	Asst	-	3	0	0	10	2	0	Good
110	Sudakar	38	M	142142	7	Drug	-	-	DG	N	N	N	N	+	Asst	-	2	1	1	12	4	2	Good
111	Ramu	22	M	142089	12	Drug	+	-	Wheal	N	N	N	N	+	Dapsone	-	2	1	0	7	2	1	Good
112	Vidya	29	F	69738	4.5	-	-	Hypothy	Wheal	N	N	N	N	-	Metho	-	3	1	1	6	3	1	Good
113	Mumtaz	26	F	69309	5	Infection	-	-	Wheal	Infection	N	N	N	-	Asst	-	2	0	0	11	5	2	Good
114	Raji	35	F	61381	2.5	Drug	-	Hypothy	Wheal	N	N	N	N	+	Control	-	4	3	2	16	14	11	Poor
115	Rajeswari	27	F	69758	10	-	-	-	Wheal	N	N	N	N	-	Asst	-	2	1	0	8	1	0	Good
116	Sumathra	21	F	16966	12	-	-	Hypothy	Papule	N	N	N	N	+	Metho	-	4	2	1	16	8	4	Average
117	Kumar	36	M	84314	13	Inhalant	+	DM	Plaque	N	Es	N	N	-	Control	-	3	1	1	9	6	5	Average
118	Shafiya	22	F	70112	8	-	-	-	Plaque	N	N	N	N	-	Dapsone	-	3	1	1	10	5	2	Good
119	Prasad	47	M	84188	10	-	+	BA	Wheal	N	N	N	N	-	Dapsone	-	5	3	2	12	6	5	Average
120	Balaji	38	M	64006	6	Food	+	HTN	Wheal	N	N	N	N	-	Control	-	3	2	3	14	10	12	Poor

KEY :

DM - - Diabetes Mellitus

HTN - - Hypertension

Hypothy - - Hypothyroidism

DG - - Dermographism

An - - Anemia

Es - - Esonophilia

ASST - - Autologous serum skin test/therapy

UAS - - Urticarial Activity Score

DLQI - - Dermatological Life Quality Index